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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Art Unit 1644

Re: U.S. Utility Patent Application
Application No. 10/662,431; Filed: September 16, 2003
For: **Apoptosis Inducing Molecule I**
Inventor: Steven M. RUBEN
Our Ref: 1488.1890004/EJH/SAC

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Credit Card Payment Form (PTO-2038);

2. Amendment and Reply Under 37 C.F.R. § 1.111;

3. Statement Concerning the Deposited Clone;

4. Revocation of Prior Power of Attorney and Appointment of New Attorneys of Record;

5. Petition for Extension of Time Under 37 CFR 1.136(a) (PTO/SB/22);

6. *Prima Facie* Showing of Entitlement to Judgment Under 37 C.F.R. § 41.202(d) and Showing of Compliance with 35 U.S.C. § 135(b) with Exhibits RE1-RE3, RE10-RE153, and RE157-RE158;

7. Request for Interference with a Patent Pursuant to 37 C.F.R. § 41.202(a) with Appendices A thru I;

8. First Supplemental Information Disclosure Statement;

9. A listing of the cited documents on Form PTO-1449;

10. A copy of the cited documents (AR1-AT1, AR2-AT2, AR3-AT3, AR4-AT4, AR5-AT5, AR6); and

11. Return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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EJH/SAC/jk
Enclosures

376003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 2661
Steven M. RUBEN	Art Unit: 1646
Application No.: 10/662,431	Examiner: HUYNH, PHUONG N
Filed: September 16, 2003	Atty. Docket: 1488.1890004
For: **Apoptosis Inducing Molecule I**	

Statement Concerning the Deposited Clone

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Plasmid DNA containing a clone encoding human Apoptosis Inducing Molecule I (AIM-I) was deposited under the terms of the Budapest Treaty on February 20, 1996. The deposit was made at the American Type Culture Collection, now located at 10801 University Boulevard, Manassas, Virginia 20110-2009, and was given accession number 97448. Assurance is hereby given that all restrictions on the availability to the public of the deposited plasmid will be irrevocably removed upon the granting of a patent, subject to 37 C.F.R. § 1.808(b).

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Date: February 22, 2005

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327322

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2661
Steven M. RUBEN	Art Unit: 1644
Appl. No.: 10/662,431	Examiner: HUYNH, PHUONG N.
Filed: September 16, 2003	Atty. Docket: 1488.1890004/EJH/SAC
For: **Apoptosis Inducing Molecule I**	

REQUEST FOR INTERFERENCE WITH A PATENT PURSUANT TO 37 C.F.R § 41.202(a)

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 41.202(a), Applicant hereby requests that an interference be declared on the subject matter of RUBEN PROPOSED COUNT A (attached as Appendix A) between the above-captioned application and U.S. Patent No. 6,521,228 issued February 18, 2003 to Wiley *et al.* (Appendix B). Concurrently herewith, Applicant is filing in this application a *Prima Facie* Showing of Entitlement to Judgment Under 37 C.F.R. § 41.202(d) and Showing of Compliance With 35 U.S.C. § 135(b), which demonstrates *prima facie* entitlement to judgment based on priority of invention under 35 U.S.C. § 102(g) relative to the patentee, and that the requirements of 35 U.S.C. § 135 have been met.

I. BACKGROUND

Ruben's captioned Application No. 10/662,431 ("the '431 application") filed September 16, 2003 is a divisional of Application No. 08/816,981, filed March 13, 1997 which claims the benefit under 35 U.S.C. § 119(e) of provisional Application No. 60/013,405 filed March 14, 1996 ("the '405 application").

Wiley *et al.* ("Wiley") Patent No. 6,521,228 ("the '228 patent") issued on February 8, 2003 from Application No. 09/825,563, filed April 2, 2001, which is a divisional of Application No. 09/320,424, filed May 26, 1999, now U.S. Patent No. 6,284,236, which is a continuation-in-part of Application No. 09/190,046, filed November 10, 1998, now abandoned, which is a continuation-in-part of Application No. 09/048,641, filed March 26, 1998, now abandoned, which is a continuation-in-part of Application No. 08/670,354, filed June 25, 1996, now U.S. Patent No. 5,763,223, which is a continuation-in-part of Application No. 08/548,368, filed November 1, 1995, now abandoned, which is a continuation-in-part of Application No. 08/496,632, filed June 29, 1995, now abandoned ("the '632 application").

II. REQUEST FOR INTERFERENCE WITH A PATENT

A. 37 C.F.R. § 41.202(a)(1)

Under the provisions of 37 C.F.R. § 41.202(a)(1), Applicant seeks to have an interference declared between pending claims 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27 of the captioned application and claims 1-35 of unexpired Wiley Patent No. 6,521,228 issued February 18, 2003 (Appendix B).

B. 37 C.F.R. § 41.202(a)(2)

Applicant proposes RUBEN PROPOSED COUNT A (Appendix A). RUBEN PROPOSED COUNT A recites:

An isolated antibody that specifically binds a protein consisting of (a) amino acids 1-281 of SEQ ID NO:2; or (b) amino acids 39-281 of SEQ ID NO: 2.

Claims of a patent or an application are presumed to correspond to a count if "the subject matter of the count, treated as prior art to the claim, would have anticipated or rendered obvious the subject matter of the claim. 37 C.F.R. § 41.207(b)(2).

1. Wiley Claims that Correspond to the Count

Claims 1-35 of the Wiley '228 patent correspond to RUBEN PROPOSED COUNT A. Claims 1-35 are drawn to anti-TRAIL antibodies, antigen-binding fragments thereof, hybridomas that produce the claimed antibodies and pharmaceutical compositions comprising anti-TRAIL antibodies. Amino acids 1 to 281 of SEQ ID NO:2 recited in the '228 patent claims are 100% identical to amino acids 1 to 281 of SEQ ID NO:2 of the captioned application. For clarity, the Wiley sequence of the '228 patent will be referred to as "SEQ ID NO:2 (Wiley)," and the Ruben sequence will be referred to as "SEQ ID NO:2 (Ruben)." These polypeptides are referred to as AIM-I by Ruben and TRAIL by Wiley.

The independent claims of the '228 patent, *i.e.*, claims 1, 13, 20 and 26, recite antibodies that bind TRAIL or a polypeptide fragment of all or a portion of the extracellular domain of TRAIL. Claim 1 of the '228 patent is the same patentable invention as proposed in Count A as both recite the same genus of anti-TRAIL antibodies. Since additional distinguishing or surprising characteristics are not shown, the antibodies recited in claims 13, 20 and 26 that specifically bind a portion of the extracellular domain, are obvious over the genus of antibodies that specifically bind the entire extracellular domain, or the entire protein. Use of the entire TRAIL protein or the extracellular domain (*i.e.*, amino acids 39 to 281) as an antigen should generate a population of antibodies, some of which should bind the extracellular fragments recited in claims 13, 20 and 26. Moreover, the ordinarily skilled artisan would have been motivated to produce antibodies against the extracellular portion of TRAIL since that is the portion accessible to antibody binding *in vivo*.

Claims 2, 5, 7, 11, 12, 14, 17, 19, 21, 25, 27 and 33 of the '228 patent specify that the antibody is a monoclonal antibody. That the antibody is a monoclonal antibody is an obvious limitation since production of monoclonal antibodies against a particular antigen is routine and, in fact, almost invariably, antibodies for therapeutic and diagnostic uses are monoclonal

antibodies. Campbell *et al.*, Monoclonal Antibody Technology, Elsevier Science, pp. 1-32 (1984) (Appendix C). Furthermore, one of ordinary skill would have been motivated, based on general knowledge possessed by those of ordinary skill of the desirability of monoclonal antibodies, to produce monoclonal antibodies. *Id.* Thus, it would have been obvious to apply routine and well known monoclonal antibody technology to produce anti-TRAIL monoclonal antibodies. As such, claims reciting monoclonal antibodies are not separately patentable from proposed Count A and should be designated as corresponding to proposed Count A.

Claims 3, 4, 15, 16, 22, 23, 28 and 29 of the '228 patent recite anti-TRAIL antibodies that either inhibit TRAIL-mediated apoptosis of a target cell or binding of TRAIL to a target cell. Antibodies against TRAIL, at an appreciable frequency, would be expected to block TRAIL activities such as apoptosis and target cell binding. Smith *et al.*, The TNF Receptor Superfamily of Cellular and Viral Proteins: Activation, Costimulation and Death," *Cell 76*: 959-962 (1994) (Appendix D). Moreover, one of ordinary skill in the art would have reasonably expected TRAIL to have apoptotic activity based on the knowledge of sequence homology and thus would have been motivated, based on the known importance of apoptosis in human disease, to generate and screen for antibodies that inhibit TRAIL-mediated apoptosis and block the binding of TRAIL to its receptor. Gruss, H-J and Dower S.K., *Blood 85*:3378-3404 (1995) (Appendix E). Accordingly, it would have been obvious to generate and screen for antibodies that inhibit TRAIL activity and these claims should be designated as corresponding to proposed Count A.

Claims 6, 7, 12, 17, 24, 30 and 34 of the '228 patent recite antigen-binding fragments of the antibodies recited by the claims discussed above. The production of an antigen-binding fragment of an antibody, such as Fab fragments, F(ab') fragments, etc., either by proteolysis with enzymes known to cleave antibody molecules resulting in antigen-binding fragments, or by genetic engineering using a cloned nucleic acid encoding a particular

antibody, was highly routine and well known in the art. Harlow, E. and D.P. Lane, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, pages 626-631 (1988) (Appendix F). Moreover, one of ordinary skill in the art would understand the utility of antigen-binding antibody fragments, and would have been motivated to make antigen-binding fragments of antibodies by highly routine and known methods. *Id.* Accordingly, these antigen-binding fragments are not separately patentable over the antibodies of proposed Count A; thus, these claims should be designated as corresponding to proposed Count A.

Finally, claims 8-10, 18, 31, 32 and 35 of the '228 patent relate to hybridomas that secrete the foregoing monoclonal antibodies and pharmaceutical compositions comprising the antibodies recited in claims 1 and 2. As discussed above, monoclonal antibody technology was well known and routine and, therefore, it would have been obvious to produce monoclonal antibodies against the TRAIL protein. Accordingly, the hybridomas that secrete those monoclonal antibodies are likewise obvious. *See* Appendix C. And, as TRAIL is a TNF ligand family member, which family was known in the prior art to have potential therapeutic uses in humans based on its sequence homology, (*See* Appendix D), the skilled artisan would have been motivated, based on the pharmacological applications of such antibodies, to formulate antibodies against TNF ligand family member polypeptides, such as TRAIL, as diagnostic or pharmaceutical compositions. Accordingly, claims 8-10, 18, 31, 32 and 35 should be designated as corresponding to proposed Count A.

Table 1, a claim chart comparing claims 1-35 of the '228 patent to Ruben Proposed Count A, demonstrates how each of these claims corresponds to the proposed count as required under 37 C.F.R. § 41.202(a)(2):

TABLE 1

'228 Patent Claims	**Limitation in Ruben Proposed Count A**
1. An antibody that specifically binds the human tumor necrosis factor related	This claim would be anticipated by Ruben Proposed Count A, because the protein

apoptosis inducing ligand (TRAIL) protein of SEQ ID NO:2.	encoded by SEQ ID NO:2 (Ruben), as recited in Ruben Proposed Count A is 100% identical to the protein encoded by SEQ ID NO:2 (Wiley). So any antibody that specifically binds this protein would inherently be the same patentable invention.
2. An antibody according to claim 1, wherein said antibody is a monoclonal antibody.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the desirability of monoclonal antibodies possessed by those of ordinary skill, to produce monoclonal antibodies against the TRAIL protein of SEQ ID NO: 2.
3. An antibody of claim 1, wherein the antibody inhibits TRAIL-mediated apoptosis of a target cell.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill in the art would have reasonably expected TRAIL to have apoptotic activity based on sequence homology, and thus would have been motivated, based on the known importance of apoptosis in human disease, to generate and screen for antibodies that inhibit TRAIL activity.
4. An antibody of claim 1, wherein the antibody blocks binding of TRAIL to a target cell.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill in the art would have had knowledge of the function of TRAIL, and thus would have been motivated, based on the general knowledge of the function of TRAIL, to generate and screen for antibodies that block the binding of TRAIL to a target cell.
5. An antibody of claim 4, wherein said antibody is a monoclonal antibody.	See claim 2.
6. An antigen-binding fragment of an antibody of claim 1.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would understand the utility of antigen-binding antibody fragments, and would have been motivated to make antigen-binding fragments of antibodies by highly routine and known methods.
7. An antigen-binding fragment of a monoclonal antibody of claim 5.	See claim 6.
8. A hybridoma cell line that produces a monoclonal antibody of claim 2.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated to produce monoclonal antibodies against SEQ ID NO:2. (see claim 2). Accordingly, hybridoma cell lines that produce such

	monoclonal antibodies would be likewise obvious.
9. A composition comprising an antibody of claim 1, and a physiologically acceptable carrier, diluent, or excipient.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill in the art would have been motivated to make such a composition, based on the pharmaceutical applications of such antibodies.
10. A composition comprising a monoclonal antibody of claim 2, and a physiologically acceptable carrier, diluent, or excipient.	See claim 9.
11. An antibody of claim 3, wherein said antibody is an monoclonal antibody.	See claim 2.
12. An antigen-binding fragment of a monoclonal antibody of claim 11.	See claim 6.
13. An antibody that specifically binds a soluble human TRAIL polypeptide, wherein said polypeptide comprises amino acids x to 281 of SEQ ID NO:2, wherein x represents an integer from 39 to 95.	This claim would be anticipated by Ruben Proposed Count A, because amino acids 39 to 281 of SEQ ID NO:2 (Ruben), as recited in Ruben Proposed Count A are identical to the recited polypeptide when x=39, so isolated antibodies that specifically bind these identical amino acids would be the same patentable invention.
14. An antibody of claim 13, wherein said antibody is a monoclonal antibody.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the desirability of monoclonal antibodies possessed by those of ordinary skill, to produce monoclonal antibodies against amino acids 39-281 of SEQ ID NO:2 since the extracellular portion is the portion accessible to antibody binding *in vivo*.
15. An antibody of claim 13, wherein the antibody inhibits TRAIL-mediated apoptosis of a target cell.	See claim 3.
16. A monoclonal antibody of claim 14, wherein the antibody blocks binding of TRAIL to a target cell.	See claim 4.
17. An antigen-binding fragment of a monoclonal antibody of claim 14.	See claim 6.
18. A hybridoma cell line that produces a monoclonal antibody of claim 14.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated to produce monoclonal antibodies against amino acids 39-281 of SEQ ID NO:2 since the extracellular portion is the portion accessible to antibody binding *in vivo*. (see claim 14) Accordingly, hybridoma cell lines that produce such monoclonal antibodies

	would be likewise obvious.
19. An antibody of claim 15, wherein said antibody is a monoclonal antibody.	See claim 14.
20. An antibody that binds a polypeptide comprising amino acids 124 to 276 of SEQ ID NO:2.	This claim would be rendered obvious by Ruben Proposed Count A, because the set of antibodies which bind to a polypeptide comprising amino acids 124 to 276 is a subset of the set of antibodies which bind the polypeptide comprising amino acids 39 to 281. Since both sets of antibodies bind to the extracellular portion of TRAIL, and no unique or unusual properties are ascribed to the subset, the antibodies are obvious over the genus of antibodies that specifically bind the extracellular domain.
21. An antibody of claim 20, wherein said antibody is a monoclonal antibody.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the desirability of monoclonal antibodies possessed by those of ordinary skill, to produce monoclonal antibodies against amino acids 124-276 of SEQ ID NO:2 since the extracellular portion is the portion accessible to antibody binding *in vivo*.
22. An antibody of claim 20, wherein the antibody inhibits TRAIL-mediated apoptosis of a target cell.	See claim 3.
23. A monoclonal antibody of claim 21, wherein the antibody blocks binding of TRAIL to a target cell.	See claim 4.
24. An antigen-binding fragment of a monoclonal antibody of claim 21.	See claim 6
25. An antibody of claim 22, wherein said antibody is a monoclonal antibody.	See claim 21.
26. An antibody that binds a fragment of the TRAIL protein of SEQ ID NO:2, wherein the N-terminal amino acid of said fragment is selected from residues 39 to 124 of SEQ ID NO:2, and the C-terminal amino acid of said fragment is selected from residues 276 to 281 of SEQ ID NO:2.	This claim would be anticipated by Ruben Proposed Count A, because amino acids 39 to 281 of SEQ ID NO:2 (Ruben), as recited in Ruben Proposed Count A is identical to the recited polypeptide when the N-terminal amino acid is residue 39 and the C-terminal amino acid is residue 281, so isolated antibodies that specifically bind these identical amino acids would be the same patentable invention.
27. An antibody of claim 26, wherein said antibody is a monoclonal antibody.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the desirability of monoclonal antibodies

	possessed by those of ordinary skill, to produce monoclonal antibodies against a fragment of SEQ ID NO:2, wherein the N-terminal amino acid of said fragment is selected from residues 39 to 124 of SEQ ID NO:2, and the C-terminal amino acid of said fragment is selected from residues 276 to 281 of SEQ ID NO:2 since the extracellular portion is the portion accessible to antibody binding *in vivo*.
28. An antibody of claim 26, wherein the antibody inhibits TRAIL-mediated apoptosis of a target cell.	See claim 3.
29. A monoclonal antibody of claim 27 wherein the antibody blocks binding of TRAIL to a target cell.	See claim 4.
30. An antigen-binding fragment of a monoclonal antibody of claim 27.	See claim 6.
31. A hybridoma cell line that produces a monoclonal antibody of claim 27.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated to produce monoclonal antibodies against a fragment of SEQ ID NO:2, wherein the N-terminal amino acid of said fragment is selected from residues 39 to 124 of SEQ ID NO:2, and the C-terminal amino acid of said fragment is selected from residues 276 to 281 of SEQ ID NO:2 since the extracellular portion is the portion accessible to antibody binding *in vivo*. (see claim 27) Accordingly, hybridoma cells that produce such monoclonal antibodies would be likewise obvious.
32. A hybridoma cell line that produces a monoclonal antibody of claim 29.	See claim 31.
33. An antibody of claim 28, wherein said antibody is a monoclonal antibody.	See claim 27.
34. An antigen-binding fragment of a monoclonal antibody of claim 33.	See claim 6.
35. A hybridoma cell line that produces a monoclonal antibody of claim 33.	See claim 31.

For the foregoing reasons, claims 1-35 of the Wiley '228 patent are directed to the same patentable invention as RUBEN PROPOSED COUNT A and should be designated as corresponding to that proposed count.

2. Ruben Claims that Correspond to the Count

Claims 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27 of the Ruben '431 application correspond to RUBEN PROPOSED COUNT A. Ruben's claims 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27 of the '431 application are drawn to anti-AIM-I antibodies, antigen-binding fragments thereof, hybridomas that produce the claimed antibodies and pharmaceutical compositions comprising anti-AIM-I antibodies. As indicated above, SEQ ID NO:2 (Ruben) and SEQ ID NO:2 (Wiley) share an identical amino acid sequence, i.e. they are the same protein.

The independent claims of the '431 application, i.e., claims 1, 13, 22, and 26 recite antibodies and antibody fragments that bind AIM-I or the extracellular domain of AIM-I. Claims 1, 13, and 22 of the '431 application are the same patentable invention as proposed in Count A. The antibody fragment recited in claim 26 is obvious over antibodies that specifically bind the AIM-I protein or the extracellular domain of AIM-I because one of ordinary skill in the art would understand the utility of antigen-binding antibody fragments, and would have been motivated to make antigen-binding fragments of antibodies by highly routine and known methods. *See* Appendix F.

Claims 2, 14, 20-21, 23-24 and 27 of the '431 application specify that the antibody is a monoclonal (claims 2, 14, 23, and 27), polyclonal, chimeric, humanized or a human antibody (claims 20, 21, 24, and 27). That the antibody is a monoclonal, polyclonal, chimeric, humanized or human antibody is an obvious limitation since production of these types of antibodies against a particular antigen is routine. *See* Appendix C; Ausubel *et al.*, Current Protocols in Molecular Biology 11 (1994) (Appendix G); and Wright *et al.*, *Crit Rev Immunol. 12*:125-68 (1992) (Appendix H). Furthermore, one of ordinary skill would have been motivated, based on general knowledge of the desirability of monoclonal, polyclonal, chimeric, humanized, and human antibodies possessed by those of ordinary skill, to produce

monoclonal, polyclonal, chimeric, humanized and human antibodies. *Id.* Thus, it would have been obvious to apply routine and well known technology to produce anti-AIM-I monoclonal polyclonal, chimeric, humanized, and human antibodies. As such, claims reciting these antibodies are not separately patentable from proposed Count A and should be designated as corresponding to Count A.

Claims 6, 17, 26, and 27 of the '431 application recite antigen-binding fragments of the antibodies recited by the claims discussed above. The production of an antigen-binding fragment of an antibody, such as Fab fragments, F(ab') fragments, etc., either by proteolysis with enzymes known to cleave antibody molecules resulting in antigen-binding fragments, or by genetic engineering using a cloned nucleic acid encoding a particular antibody, was highly routine and well known in the art. *See* Appendix F. Moreover, one of ordinary skill in the art would understand the utility of antigen-binding antibody fragments, and would have been motivated to make antigen-binding fragments of antibodies by highly routine and known methods. *Id.* Accordingly, these antigen-binding fragments are not separately patentable over the antibodies of proposed Count A; thus, these claims should be designated as corresponding to proposed Count A.

Finally, claims 8 and 18 of the '431 application relate to hybridomas that secrete the foregoing monoclonal antibodies and claims 9-10 relate to pharmaceutical compositions comprising the antibodies recited in claims 1 and 13. As discussed above, monoclonal antibody technology was well known and routine and, therefore, it would have been obvious to produce monoclonal antibodies against the AIM-I protein. Accordingly, the hybridomas that secrete those monoclonal antibodies are likewise obvious. *See* Appendix C. And, as AIM-I is a TNF ligand family member, which family was known in the prior art to have potential therapeutic uses in humans, (*See* Appendix D), the skilled artisan would have been motivated, based on the pharmacological applications of such antibodies, to formulate

antibodies against TNF ligand family member polypeptides, such as AIM-I, as pharmaceutical compositions. Accordingly, claims 8-10 and 18 should be designated as corresponding to proposed Count A.

Table 2, a claim chart comparing claims 1-2, 6, 8-10, 13-14, 17-18, 20-24 and 26-27 of the present application to Ruben Proposed Count A demonstrates how each of these claims corresponds to the proposed count as required under 37 C.F.R. § 41.202(a)(2):

TABLE 2

'431 Application Claims	**Limitation in Ruben Proposed Count A**
1. An isolated antibody that specifically binds a polypeptide consisting of SEQ ID NO:2.	This claim would be anticipated by Ruben Proposed Count A, because amino acids 1 to 281 of SEQ ID NO:2 (Ruben), as recited in Ruben Proposed Count A are 100% identical to amino acids 1 to 281 of SEQ ID NO:2 (Ruben). So the isolated antibodies that specifically bind these identical amino acids would be the same patentable invention.
2. The antibody according to claim 1, which is a monoclonal antibody.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the desirability of monoclonal antibodies possessed by those of ordinary skill, to produce monoclonal antibodies against SEQ ID NO:2.
6. An antigen-binding fragment of the antibody of claim 1.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would understand the utility of antigen-binding fragments, and would have been motivated to make antigen-binding fragments of antibodies by highly routine and known methods.
8. A hybridoma cell line that produces the monoclonal antibody of claim 2.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated to produce monoclonal antibodies against SEQ ID NO:2. (see claim 6) Accordingly, hybridoma cells that produce such monoclonal antibodies would be likewise obvious.
9. A composition comprising the antibody of claim 1, and a pharmaceutically acceptable carrier.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill in the art would have been

	motivated to make such a composition, based on the pharmaceutical applications of such an antibody.
10. A composition comprising the monoclonal antibody of claim 2, and a pharmaceutically acceptable carrier.	See claim 9.
13. An isolated antibody that specifically binds a polypeptide consisting of amino acids 39 to 281 of SEQ ID NO:2.	This claim would be anticipated by Ruben Proposed Count A, because amino acids 39 to 281 of SEQ ID NO:2 (Ruben), as recited in Ruben Proposed Count A are 100% identical to amino acids 39 to 281 of SEQ ID NO:2 (Ruben). So isolated antibodies that specifically bind these identical amino acids would be the same patentable invention.
14. The antibody of claim 13, which is a monoclonal antibody.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the desirability of monoclonal antibodies possessed by those of ordinary skill, to produce monoclonal antibodies against amino acids 39-281 of SEQ ID NO:2.
17. An antigen-binding fragment of the monoclonal antibody of claim 14.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would understand the utility of antigen-binding antibody fragments, and would have been motivated to make antigen-binding fragments of antibodies by highly routine and known methods.
18. A hybridoma cell line that produces the monoclonal antibody of claim 14.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated to produce monoclonal antibodies against SEQ ID NO:2. (see claim 14). Accordingly, hybridoma cells that produce such monoclonal antibodies would be likewise obvious.
20. The antibody of claim 1, which is selected from the group consisting of: (a) a polyclonal antibody; (b) a chimeric antibody; (c) a humanized antibody; and (d) a human antibody.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the desirability of polyclonal, chimeric, humanized, and human antibodies, to produce polyclonal, chimeric, humanized or human antibodies against amino acids 1-281 of SEQ ID NO:2.
21. The antibody of claim 13, which is selected from the group consisting of: (a) a polyclonal antibody; (b) a chimeric antibody;	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the

(c) a humanized antibody; and (d) a human antibody.	desirability of polyclonal, chimeric, humanized, and human antibodies, to produce polyclonal, chimeric, humanized, or human antibodies against amino acids 39-281 of SEQ ID NO:2.
22. An isolated antibody that specifically binds the polypeptide, encoded by the human cDNA contained in ATCC Deposit No. 97448.	This claim would be anticipated by Ruben Proposed Count A, because the polypeptide of amino acids 1 to 281 of SEQ ID NO:2 (Ruben), as recited in Ruben Proposed Count A is identical to the polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448 (the amino acid sequence of SEQ ID NO:2 was obtained by sequencing the cDNA of the deposited clone). So the isolated antibodies that specifically bind these identical amino acids would be the same patentable invention.
23. The antibody of claim 22, which is a monoclonal antibody.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the desirability of monoclonal antibodies by those of ordinary skill, to produce monoclonal antibodies against the polypeptide, encoded by the human cDNA contained in ATCC Deposit No. 97448.
24. The antibody of claim 22, which is selected from the group consisting of: (a) a polyclonal antibody; (b) a chimeric antibody; (c) a humanized antibody; and (d) a human antibody.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would have been motivated, based on general knowledge of the desirability of polyclonal, chimeric, humanized, and human antibodies by those of ordinary skill, to produce polyclonal, chimeric, humanized, or human antibodies against the polypeptide, encoded by the human cDNA contained in ATCC Deposit No. 97448.
26. An isolated antibody fragment, which fragment specifically binds a polypeptide consisting of SEQ ID NO:2 or the polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448.	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would understand the utility of antigen-binding antibody fragments, and would have been motivated to make antigen-binding fragments of antibodies by highly routine and known methods.
27. The antibody fragment of claim 26, which fragment is selected from the group consisting of: (a) a humanized antibody fragment; (b) a monoclonal antibody	This claim would be rendered obvious by Ruben Proposed Count A, because one of ordinary skill would understand the utility of antigen-binding antibody fragments, and would have been motivated to make antigen-binding fragments of humanized,

fragment; (c) a polyclonal antibody fragment; (d) a human antibody fragment; and (e) a Fab fragment.	monoclonal, polyclonal, and human antibodies by highly routine and known methods.

For the foregoing reasons, claims 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27 of the Ruben '431 application are directed to the same patentable invention as RUBEN PROPOSED COUNT A and should be designated as corresponding to that count.

C. Demonstration of Interfering Subject Matter as Required Under 37 C.F.R. § 41.202(a)(3)

Claims are drawn to interfering subject matter "if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party, and vice versa. Table 3 is a claim chart comparing claim 1 of the present application to claim 1 of the '228 patent.

TABLE 3

Ruben '431 Application **Claim 1**	**Wiley '228 Patent** **Claim 1**
An isolated antibody	An antibody
that specifically binds a polypeptide	that specifically binds the human tumor necrosis factor related apoptosis inducing ligand (TRAIL) protein
consisting of SEQ ID NO:2.	of SEQ ID NO:2.

Claim 1 of the Wiley '228 patent and claim 1 of the Ruben '431 application are drawn to the same identical invention. As indicated above, AIM-I and TRAIL are two synonyms for the same protein. Furthermore, SEQ ID NO:2's are identical for the Wiley '228 patent and the Ruben '431 application. Therefore, the claims are both directed toward antibodies that

specifically bind the same protein. Accordingly, claim 1 of the Wiley '228 patent would anticipate claim 1 of the Ruben '431 application and claim 1 of the '431 application would anticipate claim 1 of the Wiley '228 patent.

For the foregoing reasons, at least one claim of the Ruben '431 application and at least one claim of the '228 patent recite interfering subject matter as required under 37 C.F.R. § 41.203(a)(3).

D. 37 C.F.R. § 41.202(a)(4)

A detailed analysis of why the Applicant will prevail on priority is found in the accompanying *PRIMA FACIE* SHOWING OF ENTITLEMENT TO JUDGMENT Pursuant to 37 C.F.R. § 41.202(d).

E. 37 C.F.R. § 41.202(a)(5)

All of Applicant's claims 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27 were pending in the captioned '431 application. In addition, Table 4 is a claim chart showing that the present claims of the '431 application do not differ from the earlier claims of the 09/327,620 application (the '620 application), filed June 8, 1999, now abandoned, which is a continuation of the '981 application (the immediate parent of the '431 application), in any material limitation.

TABLE 4

Ruben '620 Application Claim 486	**Ruben '431 Application Claim 1 and Claim 22**
486. An antibody specific to	1. An isolated antibody that specifically binds
the polypeptide of SEQ ID NO:2 or	a polypeptide consisting of SEQ ID NO:2.
	22. An isolated antibody that specifically binds the polypeptide,
the polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448	encoded by the human cDNA contained in ATCC Deposit No. 97448.

Claim 486 of the '620 application recites an antibody specific to the polypeptide of SEQ ID NO:2 or the polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448. This claim is identical to claims 1 and 22 of the present '431 application. Claim 1 recites an isolated antibody that specifically binds a polypeptide comprising SEQ ID NO:2. Claim 22 recited an isolated antibody that specifically binds the polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448. SEQ ID NO:2 of the '620 and '431 applications are identical.

Accordingly, substantially similar claims to all of Applicant's claims 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27 were previously pending in the '620 application, which is a continuation of the immediate parent of the '431 application Accordingly, no showing is required under Rule 202(a)(5) with respect to those claims.

F. 37 C.F.R. § 41.202(a)(6)

Disclosure demonstrating constructive reduction to practice for each limitation recited in Ruben's Proposed Count A is found in Table 5.

TABLE 5

Ruben's Proposed Count A	**Support in Disclosure of '405 Application (Attached as Appendix I)**
An isolated antibody that specifically binds a protein consisting of	Page 43
(a) amino acids 1-281 of SEQ ID NO:2; or	Page 28
(b) amino acids 39-281 of SEQ ID NO: 2.	Page 28

Applicant's captioned '431 application is a divisional of Application No. 08/816,981, filed March 13, 1997 which claims the benefit under 35 U.S.C. § 119(e) of provisional Application No. 60/013,405 ("the '405 application"), filed March 14, 1996. Since both of

Applicant's priority applications have the identical specification as the '431 application, Applicant is entitled to the benefit of the filing date of the priority application for RUBEN PROPOSED COUNT A.

III. CONCLUSION

Applicant respectfully requests that an interference be declared between the captioned '431 application and the Wiley '228 patent over the subject matter of RUBEN PROPOSED COUNT A, and that claims 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27 of the captioned '431 application and claims 1-35 of the Wiley '228 patent be designated as corresponding to that count. Applicant is entitled to the benefit of the filing date of the priority application for RUBEN PROPOSED COUNT A.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Attorney for Applicant
Registration No. 42,613

Date: March 18, 2005
1100 New York Avenue, N.W.
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Attachments:

Appendix A:	RUBEN PROPOSED COUNT A
Appendix B:	Wiley *et al.*, Patent No. 6,521,228 issued February 18, 2003 ("the '228 patent")
Appendix C	Campbell *et al.*, Monoclonal Antibody Technology, Elsevier Science, pp. 1-32 (1984)
Appendix D	Smith *et al.*, The TNF Receptor Superfamily of Cellular and Viral Proteins: Activation, Costimulation and Death," *Cell 76*: 959-962 (1994)

Appendix E	Gruss, H-J and Dower S.K., *Blood 85*:3378-3404 (1995)
Appendix F	Harlow, E. and D.P. Lane, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, pages 626-631 (1988)
Appendix G	Ausubel *et al.*, Current Protocols in Molecular Biology 11 (1994)
Appendix H	Wright *et al.*, *Crit Rev Immunol. 12*:125-68 (1992)
Appendix I	Ruben U.S. Provisional Application 60/013,405, filed March 14, 1996 ("the '405 application")

APPENDIX A

RUBEN PROPOSED COUNT A

An isolated antibody that specifically binds a protein consisting of (a) amino acids 1-281 of SEQ ID NO:2; or (b) amino acids 39-281 of SEQ ID NO:2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2661
Steven M. RUBEN	Art Unit: 1644
Appl. No.: 10/662,431	Examiner: HUYNH, PHUONG N.
Filed: September 16, 2003	Atty. Docket: 1488.1890004/EJH/SAC
For: **Apoptosis Inducing Molecule I**	

PRIMA FACIE SHOWING OF ENTITLEMENT TO JUDGMENT UNDER 37 C.F.R. § 41.202(d) AND SHOWING OF COMPLIANCE WITH 35 U.S.C. § 135(b)

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 41.202(d) (Bd.R. 202(d)), and in view of the accompanying Request For Interference With A Patent Pursuant To 37 C.F.R. § 41.202(a) (the "Request"), the applicant of the application captioned above, Steven M. Ruben ("Ruben") provides evidence of *prima facie* entitlement to judgment based on priority of invention relative to Wiley *et al.* ("Wiley"), of Patent No. 6,521,228 with whom an interference is requested on the subject matter of RUBEN PROPOSED COUNT A. Ruben also demonstrates herein that the requirements of 35 U.S.C. § 135(b) have been met. This showing is based on Ruben Exhibits 1-3, 10-153 and 157-158 which are listed in Ruben Exhibit 16 (RE16).

The application captioned above claims a priority date of March 14, 1996, which is after the June 29, 1995 earliest possible effective filing date of Wiley Patent No. 6,521,228. Accordingly, Ruben is entitled to an interference pursuant to Bd.R. 202(d) upon a *prima facie* showing of invention of the subject matter of RUBEN PROPOSED COUNT A prior to June 29, 1995.

Ruben demonstrates an independent basis in this paper and the supporting documents for *prima facie* priority of invention of at least one species within RUBEN PROPOSED COUNT A before the June 29, 1995 date. More specifically, Ruben conceived of at least one species within RUBEN PROPOSED COUNT A before June 29, 1995 and was reasonably diligent from a time just prior to June 29, 1995 to either (a) an actual reduction to practice on August 31, 1995 or (b) the filing of the U.S. Provisional Application No. 60/013,405 ("the '405 priority application") on March 14, 1996 (RE52)[1], which application constituted a constructive reduction to practice of at least one species within RUBEN PROPOSED COUNT A.

I. BACKGROUND

Ruben's captioned Application No. 10/662,431 ("the '431 application") filed September 16, 2003 is a divisional of U.S. Application No. 08/816,981 ("the '981 application") (RE17), filed March 13, 1997, which claims benefit under 35 U.S.C. § 119(e) to the '405 priority application (RE52), filed March 14, 1996.

Wiley's Patent No. 6,521,228 ("the '228 patent") issued from Application No. 09/825,563, filed April 2, 2001, which is a divisional of Application No. 09/320,424, filed May 26, 1999, now U.S. Patent No. 6,284,236, which is a continuation-in-part of Application No. 09/190,046, filed November 10, 1998, now abandoned, which is a continuation-in-part of Application No. 09/048,641, filed March 26, 1998, now abandoned, which is a continuation-in-part of Application No. 08/670,354, filed June 25, 1996, now U.S. Patent No. 5,763,223 ("the '223 patent"), which is a continuation-in-part

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[1] In this document, "Ruben Exhibit" is abbreviated "RE". Reference may be made to paragraph numbers or page numbers of the Ruben Exhibits. For example, "RE3, ¶ 1-4" denotes Ruben Exhibit 3 at paragraphs 1-4, whereas "RE1, 1" denotes Ruben Exhibit 1 at page 1.

of Application No. 08/548,368, filed November 1, 1995, now abandoned, which is a continuation-in-part of Application No. 08/496,632 filed June 29, 1995, now abandoned ("the '632 application"). Accordingly, the earliest possible effective filing date of Wiley Patent No. 6,521,228 is June 29, 1995.

In the Office Action dated September 22, 2004 in connection with the Ruben '431 application, claims 1-40 were rejected under 35 U.S.C. § 102(e), as anticipated by the '228 patent, and claims 1-41 were rejected under 35 U.S.C. § 102(e), as anticipated by U.S. Patent No. 6,030,945, filed January 9, 1996, ("the '945 patent"). Furthermore, claims 1-40 were rejected under 35 U.S.C. 103(a) as being obvious over Wiley *et al.*, *Immunity 3*: 673-682 (December 1995) (hereinafter "the Wiley article") in view of several general textbooks. Copies of the '228 patent, the '945 patent, and the Wiley article are attached hereto for convenience. RE1. RE2. RE10. All other rejections and/or objections should be withdrawn in view of Applicant's accompanying Amendment and Reply Under 37 C.F.R. § 1.111.

Since the 102(e) and 103(a) rejections should be the sole remaining issues in the captioned '431 application, this showing under 37 C.F.R. § 41.202(d) also constitutes a reply in full compliance with the requirements of 37 C.F.R. § 1.111 and is responsive to the 102(e) and 103(a) rejections in the September 22, 2004 Office Action. Specifically, it is believed that this showing under 37 C.F.R. § 41.202(d) establishes conception by Ruben prior to the effective filing date of the '228 patent coupled with the diligence from just prior to Wiley's June 29, 1995 earliest possible effective date of the '228 patent to Applicant's actual or constructive reduction to practice. In addition, this showing under 37 C.F.R. § 41.202(d) also fulfills the requirements of a declaration of prior invention

under 37 C.F.R. § 1.131 sufficient to antedate U.S. Patent No. 6,030,945 and the Wiley article.

Ruben would like to bring to the Examiner's attention that the Wiley '223 patent, which is in the same family as the '228 patent, is currently involved in Patent Interference No. 105,077 ("the '077 interference") with Ruben's '981 application (RE17). The '077 interference is well into the priority briefing period. Ruben submitted the Ruben Principal Brief on the Issue of Priority on October 25, 2004. Party Wiley, predictably, has attacked Ruben's evidence as presented in the priority brief. *See, e.g.*, Wiley's Principal Brief on Priority And Derivation and Wiley's Opposition to Ruben's Principal Priority Brief. Ruben has vigorously argued that Party Wiley's opposition is without merit. *See* Ruben Reply to Wiley Opposition to Ruben Principal Brief on the Issue of Priority and Ruben Opposition to Wiley's Principal Brief on Priority and Derivation Brief filed December 16, 2004. Upon request, Applicant will provide copies of these briefs to the Examiner. The full record is being made public on March 25, 2005 and the oral hearing is likely to be scheduled for April 2005. In addition, Applicant has submitted documents to fulfill our duty of disclosure under 37 C.F.R. § 1.56 in the concurrently filed Supplemental Information Disclosure Statement.

II. SUMMARY OF RUBEN'S CASE FOR PRIORITY OF INVENTION

A. The Count -- Ruben Proposed Count A

RUBEN PROPOSED COUNT A recites:

An isolated antibody that specifically binds a protein consisting of (a) amino acids 1-281 of SEQ ID NO:2; or (b) amino acids 39-281 of SEQ ID NO: 2.

As shown in the accompanying Request under 202(a), claims 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27 of the Ruben '431 application correspond to the count and claims 1-35 of the Wiley '228 patent correspond to the count.

B. Ruben Conceived Before Wiley And Was Diligent From Just Prior to Wiley's Earliest Priority Date Until Ruben's Reduction to Practice

Ruben conceived of an isolated antibody that specifically binds a protein consisting of amino acids 1-281 or amino acids 39-281 of SEQ ID NO:2 before June 29, 1995 and was diligent from just prior to Wiley's June 29, 1995 priority date until either (a) an actual reduction to practice by at least August 31, 1995 or (b) a constructive reduction to practice of at least one species within RUBEN PROPOSED COUNT A on March 14, 1996, the filing date of Ruben's '405 priority application.

C. Ruben's Evidence Relied On To Establish His *Prima Facie* Priority Case

Ruben's demonstration of priority of invention is based on the accompanying Ruben Exhibits 1-3, 10-153, and 157-158. RE16. Except for changing the Exhibit reference numbers, and except as noted below regarding witness declarations, RE18 to RE153 and RE157 to RE158 are copies of RX2018 to RX2153 and RX2157 to RX2158 in the '077 interference. The Exhibits include the following witness declarations:

(a) Kathryn L. Beckman (RE33 and RE142);

(b) Markus Buergin (RE54);

(c) Eric Closs (RE138);

(d) Timothy Coleman (RE64 and RE143);

(e) Scott Conklin (RE18);

(f) Edward Dul (RE30 and RE144);

(g) Ann Ferrie (f.k.a. Ann M. Kim) (RE86, RE145, and RE158);

(h) Reiner L. Gentz (RE58);

(i) Solange Gentz (f.k.a. Solange H. Lima) (RE68);

(j) James Grinnell (RE56);

(k) Mark Langer (RE139);

(l) Elliot M. Olstein (RE43 and RE146);

(m) Paul Reed (RE140);

(n) Steven M. Ruben (RE102, RE147 and RE157);

(o) Kong B. Tan (RE25 and RE148);

(p) Alemseged Truneh (RE59); and

(q) Michele Wales (RE141).

The witness declarations are copies of previously executed declarations served on opposing counsel as part of the Junior Party's Evidence on the Issue of Priority and/or Derivation on June 25, 2004 in connection with the ongoing '077 interference between the Wiley '223 patent and Ruben's '981 application. An additional cover page has been added to the declarations, and Exhibit reference numbers throughout the declarations have been redacted and replaced with the Exhibit numbers referred to herein. A declaration of the undersigned attorney verifying the authenticity of the witness' declarations is also submitted as RE14.

D. Ruben's *Curriculum Vitae*

Dr. Steven M. Ruben holds a Bachelor of Science degree, a Doctor of Philosophy degree, and undertook postdoctoral training. At the time of conception and throughout

the critical period, he acted in a scientific and managerial role at Human Genome Sciences, Inc. ("HGS"). RE13 is a copy of his current *curriculum vitae*.

E. Ruben Declarants

Dr. Steven M. Ruben is named as the inventor for involved United States Patent Application No. 10/662,431. Dr. Ruben joined Human Genome Sciences, Inc. (HGS) in 1992 in the position of Scientist, a position he held until 1993. Then, he served as Associate Director of the Molecular Biology Department of HGS from 1993 to 1996, and as Director of the Molecular Biology Department from 1996 to 1998. In 1999, Dr. Ruben became Vice President, Research, and eventually became Vice President of Preclinical Discovery, the position that he held when he left HGS in March 2003. (RE157, ¶ 1).

Ann Ferrie joined HGS in March 1993 as a Research Associate under the direct supervision of Dr. Steven M. Ruben. At that time, Ms. Ferrie was known as Ann Kim. Ms. Ferrie worked as a Research Associate under Dr. Ruben's supervision until she left HGS in June 1998. (RE158, ¶ 1).

Reiner L. Gentz, Ph.D., was employed by HGS from 1993 to May 1997 in the position of Director, Protein Expression and Purification. From May 1997 to December 2000, he served at HGS as Vice President, Protein Development. (RE58, ¶ 1).

Timothy A. Coleman, Ph.D., was employed by HGS from March 1993 to November 2001. During the time period discussed below, he held the position of Scientist in the HGS Protein Expression and Purification Department, working under the supervision of Dr. Reiner Gentz. (RE143, ¶ 1).

Solange Gentz was employed by HGS from November 1993 to June 1998 and then from June 2000 through May 2002. During the period from February 1995 through

March 1996, she was a Research Associate at HGS in the Department of Protein Development. At that time, she was known as Solange H. Lima. She worked under the direct supervision of Dr. Timothy Coleman. (RE68, ¶ 1).

James Grinnell was employed by HGS in the Department of Bioinformatics/Information Technology from August 1994 to January 2004. He initially joined HGS in the position of Systems Administrator and ultimately held the position of Data Center Manager. (RE56, ¶ 1).

Kathryn L. Beckman was employed by HGS in the position of Intellectual Property Administrator in the HGS legal department from February 1995 until June 1998. Her duties included establishing and supervising the operation of HGS's patent docket system, as well as corresponding with outside counsel and HGS scientists regarding the preparation of patent applications. (RE33, ¶ 1).

Alemseged Truneh, Ph.D., was employed by GlaxoSmithKline (formerly SmithKline Beecham (SB)) until September 30, 2001 and acted in a scientific and management role for SB during the time period discussed below. (RE59, ¶ 1).

Kong B. Tan is employed by GlaxoSmithKline (formerly SmithKline Beecham (SB)) and acted in a scientific role as a Senior Investigator at SB during the time periods discussed below. (RE148, ¶ 1).

Edward Dul is employed by GlaxoSmithKline (formerly SmithKline Beecham (SB)) and acted in a scientific role for SB during the time periods discussed below. (RE30, ¶ 1).

Paul Reed has been employed by GlaxoSmithKline (GSK) since 1983. During the 1994-1996 time period, he was the Director of Bioinformatics, Alliance Management. His responsibilities included handling of information transmitted

electronically between GSK (then SmithKline Beecham) and Human Genome Sciences. (RE140, ¶ 1).

Michele Wales has been employed by Human Genome Sciences, Inc. since 1998, and is currently Associate General Counsel, Patent Litigation. (RE141, ¶ 1).

Elliot M. Olstein has been a member of the law firm of Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein (Carella), of Roseland, New Jersey since 1979. During the time period encompassing 1995 and 1996, he was the partner-in-charge at Carella of Human Genome Sciences, Inc. In the 1995-1996 time period, Mr. Charles J. Herron and Mr. Gregory D. Ferraro were associates at Carella who worked on HGS matters under Mr. Olstein's supervision. (RE43, ¶ 1).

Scott Conklin has been employed by Pocono Rabbit Farm & Laboratory, Inc. (PRF&L) since 1992. During his career at PRF&L, Mr. Conklin has been closely involved in the process of raising antibodies in rabbits against proteins sent to PRF&L by its customers and providing its customers with resultant antiserum. (RE18, ¶ 1).

F. HGS Company Overview

HGS was founded in 1992 as a start-up company in the emerging field of genomics. During the critical period from just prior to June 29, 1995 to March 14, 1996, HGS was a small, young, rapidly-growing company compared to other companies developing pharmaceutical products. Nevertheless, by the commencement of the critical period, HGS had already sequenced thousands of human cDNAs to obtain a large number of proteins for potential product development. Compared to this large number of potential products, HGS had a relatively small work force for carrying out the experiments that such development requires. Significantly, AIM-I was not only one of

the select few molecules chosen for development, but it also received an exceptional amount of experimental resources even among the chosen few.

As exhaustively detailed in this showing and the supporting documents, a number of HGS scientists, SmithKline Beecham ("SB") scientists, and other contract scientists made an enormous collective effort toward the development of AIM-I leading up to and during the critical period from just prior to June 29, 1995 until either (a) an actual reduction to practice by August 31, 1995 or (b) a constructive reduction to practice on March 14, 1996. A timeline and a day-to-day calendar summarizing critical period activities which constitute Ruben's diligence are described further below and are attached hereto as RE12 and RE11, respectively.

Because AIM-I and other novel TNF ligand and receptor family members discovered at HGS were of such great interest to the young company, a joint program with SB was established to tap even greater resources. The distribution list of an October 18, 1995 joint program meeting is indicative of the exceptional amount of resources that were being devoted to developing AIM-I and other TNF/TNFR family members as potential products. *See e.g.*, Reiner L. Gentz Declaration. (RE58, ¶ 2). This joint program, directed to investigating the roles of AIM-I and other TNF ligand and TNF receptor family members in regulating cell proliferation and death, was by far the greatest scientific collaboration that HGS had undertaken since its founding in 1992.

G. HGS Clone Identification System

HGS cDNA clones are each assigned an alphanumeric identifier typically consisting of five letters followed by two numbers. HTPAN08, the clone encoding AIM-I of the present invention, is an example of such a clone identifier. Each letter and number in the identifier represents an aspect of the cDNA library from which the clone

was isolated. The first letter in a clone identifier represents the species. In the case of HTPAN08, "H" indicates the clone was derived from the human species. The second two letters in a clone identifier represent the tissue. HTPAN08 was isolated from a tumor library of pancreatic origin ("T" represents "tumor" and "P" represents pancreas). The next two letters represent the specific 96-well laboratory plate that contains the library. Each 96-well plate was assigned a two letter designation in alphabetical order (i.e., AA, AB, AC, etc.). Clone HTPAN08 was isolated from a 96-well plate designated "AN". Finally, the two numerals at the end of a clone identifier indicate which well of a 96-well plate contained the clone. Accordingly, HTPAN08 was isolated from well number "08" on plate AN of the human pancreatic tumor (HTP) library. In this manner, a clone identifier specifies exactly which library, plate, and well contains the original cDNA clone.

H. AIM-I Synonyms

AIM-I is referred to by various synonyms in this showing and the supporting documents. In the Wiley '228 patent, AIM-I is referred to as TRAIL, for *T*NF *r*elated *a*poptosis *i*nducing *l*igand. As explained above, the original clone encoding AIM-I is termed HTPAN08. Other clones encoding AIM-I include 413412 (HGS code) and ATG 343 (SB code). The AIM-I protein itself is alternatively referred to as TL2, TL-2, TNFLl, Apo2 ligand, APO-2L, and as a homologue of Fas ligand from rat ("rat Fas ligand homolog" or "Fas Ligand" or "FasLig").

I. AIM-I Cancer Therapeutics

From numerous experiments performed worldwide by a large number of laboratories in recent years, AIM-I has become quite well established in the art as having

apoptosis-inducing activity, confirming Ruben's conception. Indeed, AIM-I and derivatives and fragments thereof are considered leading candidates for therapeutic use in a number of proliferative disease settings. As evidence of the foregoing, and by way of subsequent history and background information, eight recent review articles regarding AIM-I are provided herewith (Nguyen *et al.*, 2000, *Forum (Genova) 10*, 243-52 (RE106); Schneider *et al.*, 2000, *Pharm. Acta Helv. 74*, 281-6 (RE122); Walczak *et al.*, 2000, *Exp. Cell Res. 256*, 58-66 (RE123); Roth *et al.*, 1999, *Cell. Mol. Life Sci. 56*, 481-506 (RE124); Marsters *et al.*, 1999, *Recent Prog. Horm. Res. 54*, 225-34 (RE125); Bonavida *et al.*, 1999, *Int. J Oncol. 15*, 793-802 (RE126); Griffith *et al.*,1998, *Curr. Opin. Immunol. 10*, 559-63 (RE127); and Golstein, 1997, *Curr. Biol. 7*, R750-3 (RE128)).

III. RUBEN WAS FIRST TO CONCEIVE AND WAS DILIGENT FROM JUST PRIOR TO JUNE 29, 1995 UNTIL EITHER (a) AN ACTUAL REDUCTION TO PRACTICE OR (b) A CONSTRUCTIVE REDUCTION TO PRACTICE

A. Conception

The appropriate standard of proof is proof by a preponderance of the evidence, *i.e.*, that the existence of the fact is more probable than its nonexistence. *Bruning v. Hirose*, 161 F.3d 684, 691, 48 U.S.P.Q.2d 1934, 1938 (Fed. Cir. 1998).

1. Legal Principles

Conception is "the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice." *Kridl v. McCormick*, 105 F.3d 1446, 1449, 41 U.S.P.Q.2d 1686, 1689 (Fed. Cir. 1997). To establish conception, a party must demonstrate possession of every limitation recited in the count. *See id.* Conception is complete, "when the idea is so

clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation," *Burroughs Wellcome Co. v. Barr Lab., Inc.*, 40 F.3d 1223, 1228, 32 U.S.P.Q.2d 1915, 1919 (Fed. Cir. 1994). A conception may be complete even though it requires further experimentation in order to achieve reduction to practice. *Singh v. Brake*, 222 F.3d 1362, 1367, 55 U.S.P.Q.2d 1673, 1676 (Fed. Cir. 2000).

A party seeking to prove conception through the oral testimony of an inventor must proffer evidence corroborating that testimony. *See Price v. Symsek*, 988 F.2d 1187, 1194, 26 U.S.P.Q.2d 1031, 1036 (Fed. Cir. 1993). Corroboration need not take any particular form. *See Kridl*, 105 F.3d at 1450, 41 U.S.P.Q.2d at 1689. Whether or not an inventor's testimony is adequately corroborated is determined by a "rule of reason" analysis in which "an evaluation of all pertinent evidence must be made so that a sound determination of the credibility of the inventor's story may be reached." *Price*, 988 F.2d at 1195, 26 U.S.P.Q.2d at 1037. Complete conception, however, requires at least some manifestation or disclosure of the invention. *Cislak v. Wanger*, 215 F.2d 275, 281-82, 103 U.S.P.Q. 39, 42 (CCPA 1954).

It is notable that, for a compound which is similar to compounds of known utility, corroboration of conception may be implicit. *Kridl v. McCormick*, 105 F.3d 1446, 41 U.S.P.Q.2d 1686 (Fed. Cir. 1997) ("[T]he court ... held that the appellant's evidence was sufficient to corroborate conception of the invention. In *Rey-Bellet*, the key factor was the structural similarity of the compounds of the invention to prior art compounds having a known use, thereby indicating by implication the conceived utility.") (explaining *Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 181 U.S.P.Q. 453 (C.C.P.A. 1974)).

In the context of inventions relating to chemical compounds, including nucleic acid inventions, conception requires more than an "idea of [the] compound" and a method for isolating it. *See Fiers v. Revel*, 984 F.2d 1164, 1169, 25 U.S.P.Q.2d 1601, 1604-05 (Fed. Cir. 1993). "Conception of a substance claimed per se without reference to a process requires conception of its structure, name, formula, or definitive chemical or physical properties." *Id., see also Amgen, Inc. v. Chugai Pharma. Co., Ltd.*, 927 F.2d 1200, 1206, 18 U.S.P.Q.2d 1016, 1021 (Fed. Cir. 1991) ("The subject matter was the novel purified and isolated sequence which codes for EPO . . . ."). Thus, mere research plans or hopes for obtaining a nucleic acid molecule are not sufficient. *See Fiers*, 984 F.2d at 1169, 25 U.S.P.Q.2d at 1604-05.

Specifically, in the context of inventions related to antibodies, "so long as an applicant has disclosed a 'fully characterized antigen, 'either by its structure, formula, chemical name, or physical properties . . . the applicant can then claim an antibody by its binding affinity to that described antigen." *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 U.S.P.Q.2d 1508 (Fed. Cir. 2004).

Additionally, decisions by the courts and the Board of Patent Appeals and Interferences suggest, that in order to establish conception of a chemical compound the inventor has to conceive of a practical utility for the compound. *See Rey-Bellet v. Engelhardt,* 493 F.2d 1380, 1387, 181 U.S.P.Q. 453, 457-58 (CCPA 1974); *D'Amico v. Brown*, 155 U.S.P.Q. 534, 537-38 (Bd. Pat. Int'f 1967). Conception of a practical utility for a chemical compound requires only that the inventor had formed the idea of an intended use of the compound "in sufficiently final form that only the existence of ordinary skill remained to reduce it to practice." *Burroughs Wellcome*, 40 F.3d at 1231, 32 U.S.P.Q.2d at 1922.

Conception does not require that the inventor prove by scientific experiment that the compound will work for its intended purpose. *See id.* (conception of an invention directed to 3'-azidothymidine (AZT) did not require experimental proof that AZT was effective for its intended use as an inhibitor of the human immunodeficiency virus); *see also Rey-Bellet*, 493 F.2d at 1387, 181 U.S.P.Q. at 457-58 (conception of an invention directed to nortriptyline (NTL) was complete when the inventor produced the compound and expressed a belief, based on structural similarity to other compounds, that it would have antidepressant activity, even though *in vivo* experiments had not been carried out which definitively established NTL's antidepressant activity). Thus, to prove conception of an invention, an inventor "need only show that he had the idea; the discovery that an invention actually works is part of its reduction to practice." *Burroughs Wellcome*, 40 F.3d at 1228, 32 U.S.P.Q.2d at 1919.

2. Ruben's Conception

a. Isolated Antibody That Specifically Binds AIM-I Polypeptide Was Conceived Prior to June 29, 1995

An isolated antibody that specifically binds a protein consisting of amino acids 1-281 of SEQ ID NO:2 was conceived by Dr. Ruben in the U.S. by August 17, 1994, alternatively, by January 20, 1995, alternatively, by March 15, 1995 or alternatively, by June 26, 1995. Major events leading up to the August 17, 1994, alternatively, January 20, 1995, alternatively March 15, 1995 or alternatively, June 26, 1995 conception are summarized as follows.

Prior to September 1993, a partial cDNA of AIM-I was cloned, sequenced, and designated HTPAN08 under Dr. Ruben's direction. RE158, ¶ 6. The HTPAN08 clone had already been subjected to a database search and analysis by September 20, 1993, as

indicated by reference to the clone as having similarity to TNFα. RE158, ¶ 7. On February 2, 1994, Dr. Ruben created an electronic project for HTPAN08. RE157, ¶ 6. On February 8, 1994, Dr. Ruben instructed his laboratory assistant Ann Ferrie (f.k.a. Ann M. Kim) to conduct a "BLAST"[2] search in a computer database for nucleic acid sequences having homology to HTPAN08. RE158, ¶ 9. Ms. Ferrie carried out the BLAST search of DNA sequence databases on February 9, 1994 in order to identify polypeptides having significant sequence identity and similarity to the partial polypeptide that was predicted to be encoded by the HTPAN08 clone. RE158, ¶ 9.

BLAST analysis revealed that the HTPAN08 clone shared highest sequence homology with Fas ligand, a protein primarily involved in apoptosis, and also shared significant sequence homology with TNFα and LTα, which are other members of a small and well-defined subset of the TNF ligand super family that was known to induce apoptosis. RE158, ¶ 9. RE157, ¶¶ 6-8. Thus, as early as 1994, Dr. Ruben had recognized that AIM-I is a member of a well-established class of molecules, the TNF ligand family and that it showed the highest degree of sequence homology with TNF family members that induced apoptosis (FasL, TNFα, and LTα). *See* RE157, ¶¶ 7-8. At that time, Ruben created a project dedicated to AIM-I which was part of a concerted effort among HGS and its collaborators to investigate members of the TNF ligand and TNF receptor families. RE157, ¶ 6. A clone encoding a full-length AIM-I molecule (designated HTPAN08S04) (*See* RE88 at page 67.) was isolated by March 3, 1994, and

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[2] BLAST (Basic Local Alignment Search Tool) provides a method for rapid searching of nucleotide and protein databases.

by June 20, 1994 the full-length nucleotide sequence had been determined and entered into IRIS[3]. *See* RE158, ¶¶ 10, 12.

Working under Dr. Ruben's direction, and by August 8, 1994, Ms. Ferrie had corrected minor sequencing errors and entered the corrected sequence into the computer and printed out a translation of a full-length nucleotide sequence encoding amino acids 1 to 281 of SEQ ID NO:2. RE157, ¶ 12. RE158, ¶ 13. The corrected sequence was later designated HTPAN08XY and again was entered into IRIS on November 15, 1994. RE158, ¶ 16. The nucleotide sequence encoding AIM-I printed out by Ms. Ferrie on August 8, 1994 and the corresponding amino acid sequence of AIM-I correspond to the AIM-I nucleotide and amino acid sequences disclosed in Figure 1 of Provisional Application No. 60/013,405, filed March 14, 1996. RE157, ¶ 12.

On August 9, 1994 under Dr. Ruben's direction, Ms. Ferrie performed a BLAST analysis of the full-length, corrected AIM-I amino acid sequence which confirmed significant similarity between AIM-I and several species of Fas ligand and TNFα proteins. RE158, ¶ 15. RE157, ¶ 13. On August 10, 1994 the complete amino acid sequence of AIM-I was aligned with several other members of the TNF ligand family to highlight the regions of homology among the proteins. RE157, ¶ 14. Dr. Ruben and Ms. Ferrie discussed the results by August 17, 1994. RE157, ¶ 14. RE158, ¶ 15. Dr. Ruben and Reiner Gentz discussed around this same time and certainly by January 20, 1995 that because of the significant degree of homology of AIM-I to FasL and TNFα, HGS should pursue the development of AIM-I based therapeutics including AIM-I antibodies, for example for the treatment of autoimmune diseases. RE58, ¶ 5. RE157, ¶15. Once the AIM-I protein was obtained, nothing more than ordinary skill would be required to

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[3] HGS's electronic database.

produce an antibody encompassed by the count, therefore, these activities clearly demonstrate that Dr. Ruben had conceived of a complete and operative invention by August 17, 1994 or alternatively, January 20, 1995. RE157 ¶ 15. RE58, ¶ 5.

In late September 1994, Ms. Ferrie began working, under Dr. Ruben's supervision, on a bacterial expression construct for the AIM-I protein. RE158, ¶ 48. RE157, ¶ 23. Dr. Ruben told Ms. Ferrie that bacterial expression of AIM-I was important for providing an abundant source of AIM-I antigen for the production of anti-AIM-I antibodies. RE158, ¶ 48. RE157, ¶ 25. The AIM-I protein produced by this bacterial expression construct was later used as an antigen for producing isolated antibodies encompassed by Ruben's Proposed Count A. By February 1, 1995, Ms. Ferrie confirmed that the DNA encoding AIM-I was properly inserted into the bacterial expression vector. RE158, ¶ 89. Ms. Ferrie then worked under the direction of Dr. Ruben to use the expression construct to produce the AIM-I protein in bacteria. On March 8, 1995, Ms. Ferrie prepared a culture of bacteria to express AIM-I. On March 9, 1995, Ms. Ferrie used IPTG to induce expression of the AIM-I protein in bacteria and then she harvested the bacteria. RE158, ¶¶ 127-28.

On March 10, 1995, Ms. Ferrie carried out polyacrylamide gel electrophoresis (PAGE) of proteins obtained in the cell cultures from the previous day's induction experiments and the PAGE analysis indicated that the AIM-I protein had been successfully produced. The protein was then purified by column chromotography. RE158, ¶ 129. Thus, by March 15, 1995, Dr. Ruben had directed Ms. Ferrie to (i) subclone the isolated nucleic acid encoding the polypeptide of SEQ ID NO:2 (*i.e.*, AIM-I) into a bacteria expression vector, (ii) express AIM-I protein in bacteria, and (iii) purify

AIM-I protein for antibody production by both column chromatography and by preparative gel electrophoresis.

In addition, beginning on May 8, 1995 and working under the direction of Dr. Ruben, Ms. Ferrie prepared a culture of bacteria containing a full-length AIM-I expression construct. RE158, ¶ 131. Ms. Ferrie induced expression of AIM-I in these bacteria on May 12, 1995, and then column purified the AIM-I protein. RE158, ¶ 134. She then provided the protein to the Protein Expression Department of HGS for preparation of a renaturation column. RE158, ¶ 137. On May 23, 1995, Ms. Ferrie received back the renaturation column from the Protein Expression Department, on which day she also eluted the renatured AIM-I protein with imidazole elution buffer and performed PAGE analysis of the eluted AIM-I protein. RE158, ¶ 138.

Between March 8, 1995 and March 15, 1995, and on June 26, 1995, under the direction of Dr. Ruben, Ms. Ferrie engaged in experiments to express and purify AIM-I protein from bacterial cells using IPTG induction in order to purify AIM-I for AIM-I antibody production. RE158, ¶¶ 156-160. RE157, ¶ 31. On March 15, 1995, the AIM-I protein, produced by bacterial expression on March 10, 1995, was isolated from a preparative gel slice. RE158, ¶ 159. Ms. Ferrie, in her notebook, indicated that the isolated AIM-I protein was "[r]eady for Ab production." RE92, page 72. On June 26, 1995, a sample of the AIM-I protein was sent to Pocono Rabbit Farm and Laboratory (PRF&L) for anti-AIM-I antibody production. RE158, ¶ 160. RE157, ¶ 31. In her letter dated June 26, 1995 to Cindy Haab of PRF&L, in which she referred to AIM-I as "FasLig," Ms. Ferrie requested that PRF&L produce anti-"FasLig" antibodies by its standard protocol for fusion protein antigens. RE158, ¶ 160. Having obtained the purified AIM-I protein, nothing more than ordinary skill would be required to produce an

antibody encompassed by the count. These activities clearly demonstrate that Dr. Ruben had alternatively conceived of a complete and operative invention by at least March 15, 1995 or alternatively, June 26, 1995.

b. Utility of Anti-AIM-I Antibodies

On February 2, 1994, Dr. Ruben created an electronic project for HTPAN08 (RE97), subsequently revising it on April 14, 1995 (RE99). Specifically, the entry under "POTENTIAL COMMERCIAL VALUE" on the Project Worksheet created on February 2, 1994 (RE97) indicates that clone HTPAN08 encodes " . . . a potential cytokine with some homology to TNF alpha. TNF alpha has cytotoxic properties against several tumor lines." (RE97 at page 1). On February 8, 1994, Dr. Ruben's laboratory assistant Ann Ferrie entered the results of a BLAST protein database search (using the C-terminus of AIM-I) into the HGS IRIS Project Worksheet database. The BLAST results of the HTPAN08-encoded protein shown in that project worksheet indicate a high degree of homology with rat Fas ligand, TNF-α, and lymphotoxin beta, members of the TNF ligand family that induce apoptosis[4]. (RE98). The February 8, 1994 entry was backed up on a magnetic tape dated April 29, 1994. RE98. Dr. Ruben reviewed Ms. Ferrie's work on a regular basis, as described. RE157, ¶ 4. The BLAST results were communicated to Dr. Ruben on or about February 9, 1994. Dr. Ruben's analysis of the BLAST results in February 1994 clearly indicated to him that given that AIM-I has the greatest similarity to Fas ligand and TNFα, TNF ligand family members known to induce apoptosis, AIM-I would also have apoptosis inducing activity. RE157, ¶ 7. Dr. Ruben

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[4] Apoptosis, or programmed cell death, is a specific cellular self-termination protocol which is distinct from necrotic cell death and is characterized by DNA fragmentation or "laddering" and other hallmarks." RE157, ¶8. This protocol is triggered by a subset of ligands within the TNF ligand family. Prototypic examples of such ligands known to induce apoptosis are Fas ligand, TNFα, and LTα. RE157, ¶8.

communicated to Ms. Ferrie his interest in pursuing the protein encoded by HTPAN08 as "an apoptosis inducing agent for developing therapeutics, *e.g.*, to treat cancer", and instructed her to screen the HTP cDNA library from which the original HTPAN08 clone was isolated for a full-length cDNA clone. RE158, ¶9.

Dr. Ruben was aware of references that indicated that the TNF ligand family members could induce apoptosis. "Abundant evidence existed at least as early as 1994 to inform scientists of the well-defined nature of the TNF ligand family." RE157, ¶ 8. Most significantly, a *Minireview* in the journal *Cell* by Smith *et al.* dated March 25, 1994 and entitled "The TNF Receptor Superfamily of Cellular and Viral Proteins: Activation, Costimulation, and Death" clearly set forth the characteristics of "12 receptors [that] have been identified (Figure 1) with which we can associate some eight TNF-related cytokines (Figure 2)." *See* Smith *et al.*, 1994, *Cell 76*, 959-962 ("Smith") at page 959, column 1, ¶ 2, and at Figures 1 and 2. (RE3). One of the reasons the TNF ligand family is so well established is because TNFα and TNFβ (*a.k.a.* lymphotoxin or LTα) were among the very first cytokines to be molecularly cloned and sequenced in 1984. *Id.* at page 959, column 1, ¶ 1. (RE3). Subsequent to this landmark event, the TNF ligand family underwent a full decade of intensive study and development prior to Ruben's discovery of AIM-I in 1994. Indeed, by 1994, Smith had concluded that "[t]he contingent ability to induce death is rather unique to [the TNF ligand] family and is well established for TNFα, LTα, and FasL." (Emphasis added). *See id.* at page 962, column l, last ¶. (RE3).

Ruben testified that "additional evidence existed at least as early as 1994 demonstrating that the TNF ligand family contained members, such as Fas Ligand and TNFα, capable of triggering apoptosis." RE157, ¶ 9. For example, Figure 1 on page 16

of Sachs and Lotem (1993, *Blood 82*, 15-21) lists TNF and antibodies to Fas antigen (APO-1) as among the known inducers of apoptosis at that time. (RE107). *See also* Suda et al., 1993, *Cell 75*, 1169-1178 (*e.g.* Figure 7) (RE108); Cosman, 1994, *Stem Cells 12*, 440-455 (*e.g.* Figures 1 and 2) (RE109); Nagata, 1994, *Phil. Trans. R. Soc. Lond., Series B: Biol. Sci. (England) 345*, 281-287 (*e.g.* Figures 1 and 3) (RE110); Nagata, 1994, *Adv. Immunol. 57*, 129-144 (*e.g.* Figures 1 and 3) (RE111); Schulze-Osthoff, 1994, *Trends Cell Biol. 4*, 421-426 (*e.g.* Figures 1 and 2) (RE112); Singer *et al.*, 1994, *Curr. Opin. Immunol. (England) 6*, 913-920 (RE113); Nagata, 1994, *Semin. Immunol. 6*, 3-8 (*e.g.* Figure 1) (RE114); and Nagata *et al.*, 1995, *Science 267*, 1449-1456 (*e.g.* Figure 1) (RE115).

Moreover, considerable insight had been achieved at the time of the invention into the specific functioning of certain ligand-receptor pairs within the superfamilies, as evidenced by the following references. RE157, ¶ 10. *See* Watanabe-Fukunaga, 1992, *Nature 356*, 314-317 (RE116); Cohen *et al.*,1992, *Immunol. Today 13*, 427-428 (RE117); Crispe, 1994, *Immunity 1*, 347-349 (RE118); Lynch *et al.*, 1994, *Immunity 1*, 131-136 (RE119); Takahashi *et al.*, 1994, *Cell 76*, 969-976 (RE120); and Nagata *et al.*, 1995, *Immunol. Today (England) 16*, 39-43 (RE121).

The *Smith Minireview* was authored by three individuals, one of whom, Raymond G. Goodwin, is a patentee on the '228 patent. Accordingly, it is beyond dispute by patentee that apoptosis-inducing activity of certain members in the TNF ligand family was well established in 1994. In view of the significant sequence similarity of AIM-I to FasL, TNFα, and LTα, Dr. Ruben recognized that AIM-I would also have apoptotic activity.

Among the TNF ligand family members, all except LTα share a prototypic pro-TNFα architecture, *i.e.* type II membrane protein topology with an extracellular C-terminus, an intracellular N-terminus, and a single transmembrane domain. *Id.* at page 959, column 2, last ¶. (RE3). Moreover, the greatest sequence similarity is restricted to about 150 residues in the C-terminal region of each ligand. *Id.* at sentence bridging pages 959-960. (RE3, 1-2). The percent identity of the human AIM-I extracellular C-terminal domain to the four most closely related members of the TNF ligand family (i.e., Fas ligand, TNFα, LTα, and LTβ is 28%, 23%, 23%, and 22%, respectively. (RE3, 4). Accordingly, the similarity of AIM-I to the TNF ligand family members with well established apoptosis-inducing activity, as shown by the BLAST search results recorded by Ruben in the HGS electronic database in February 1994, provided clear evidence to Ruben that AIM-I induced apoptosis.

Ruben's BLAST analysis in February 1994 indicated that Fas ligand, a molecule primarily known to induce apoptosis, is the molecule within the TNF ligand family having the greatest similarity to AIM-I. RE157, ¶ 7. "Indeed, after rat Fas ligand, the next nearest "hits" in the BLAST search results were all to various forms of TNFα, another TNF ligand family member that was known to induce apoptosis." RE157, ¶ 7. The ninth nearest hit was CD30, another TNF ligand family member. No non-TNF ligand family member hits were detected with homology scores equal to or greater than CD30.

Ann Ferrie and Dr. Ruben also performed alignments in late July and early August of 1994 which further supported the predicted activity of AIM-I and its membership in the TNF ligand family. RE157, ¶¶ 6 and 12-14. RE158, ¶¶ 9-15. On August 8, 1994, Ms. Ferrie printed out a translation of a full-length nucleotide sequence

for HTPAN08XX. On August 9, 1994, Dr. Ruben instructed Ms. Ferrie to perform a BLAST analysis of the HTPAN08 amino acid sequence which revealed significant degrees of similarity between AIM-I and several species of TNF alpha and Fas ligand proteins. On August 10, 1994, Dr. Ruben directed Ms. Ferrie in aligning the AIM-I protein amino acid sequence with several other members of the TNF ligand family to highlight the regions of homology among the proteins (including Fas ligand, TNFα, TNFβ, and HUVE091). These results confirmed for Dr. Ruben that the AIM-I protein encoded by HTPAN08SO4 was a full-length member of the TNF ligand family with a significant degree of homology to FasL and TNFα, and, like those two proteins, would be useful in inducing apoptosis in certain cells and in treating cancer, and that antibodies to the AIM-I protein would be useful in treating autoimmune disease. RE157, ¶¶ 6 and 12-15. *See also* RE158, ¶¶ 9-15.

c. Corroboration of Ruben's Conception

The testimony of Dr. Ruben as to his complete conception is independently corroborated by the testimony of Ms. Ferrie, who carried out the sequence analysis, bacterial expression experiments, and protein purification experiments described above. Additionally, Dr. Ruben's testimony is corroborated by Ms. Ferrie's laboratory notebook records. RE87-95

Dr. Ruben's testimony is further corroborated by the testimony of Dr. Reiner Gentz, who was Director, Protein Expression and Purification during the time period of 1993-1997. RE58, ¶ 1. Dr. Gentz testified that by January 20, 1995, it was known to scientists at HGS that Dr. Ruben had cloned and isolated a nucleic acid encoding AIM-I, and that AIM-I was known to be highly homologous to key apoptosis-inducing members of the TNF ligand super family, Fas ligand and TNF-α. RE58, ¶¶ 3, 5. Dr. Gentz further

testified that he recalled discussing with Dr. Ruben around August 17, 1994 and at least by January 20, 1995 that "because of the high degree of homology of AIM-I to TNF-α and FasL, HGS should pursue the development of AIM-I based therapeutics, including anti-AIM-I antibodies, for example for the treatment of autoimmune diseases, or the AIM-I protein itself, for example, for the treatment of cancer." RE58, ¶ 5.

Dr. Ruben's testimony regarding his sequencing work is also corroborated by the testimony of James Grinnell, a former HGS employee in the Department of Bioinformatics/Information Technology. RE56, ¶ 1. Mr. Grinnell testified that the computer records of HGS included an electronic "project worksheet" that had last been modified on April 14, 1995, which is provided as RE99. RE56, ¶¶ 3-6. The authenticity of these computer tapes is confirmed by the testimony of Eric Closs and Mark Langer. RE138, ¶¶ 2-3. RE139, ¶¶ 2-3. This project worksheet contains BLAST results for the HTPAN08 clone and indicates that the encoded protein would be useful in inducing apoptosis, further evincing Dr. Ruben's complete conception prior to June 29, 1995. RE56.

Dr. Ruben's testimony is further corroborated by the testimony of Scott Conklin. RE18. Mr. Conklin testified that a letter, dated June 26, 1995, was sent from Ann Ferrie to Cindy Haab of Pocono Farms, enclosing two tubes of "FasLig" protein, for antibody production, and requesting that Pocono Farms produce anti-"FasLig" antibodies by its standard protocol for fusion protein antigens. RE18. The letter was stamped as having been received by Pocono Farms on June 28, 1995. RE24.

Dr. Ruben's testimony is further corroborated by the testimony of Paul Reed. RE140. Mr. Reed testified that collaborators at SmithKline Beecham (SB) were instructed that Dr. Ruben was the contact at HGS regarding the clone HTPAN08, which

had been provided to SB. RE140, ¶ 6. Additionally, Mr. Reed testified that Peter Young of SB submitted a request on July 1, 1994 for sequencing of the HTPAN08 clone provided to SB by HGS. RE140, ¶ 6. As was explained by declarant Alemseged Truneh, a former scientist and manager at SB, the results of the sequencing request by Mr. Young provide independent corroboration of the full-length AIM-I sequence (also known as TL2) that had been obtained by Dr. Ruben from the HTPAN08SO4 clone. RE59, ¶ 5.

d. Summary of Complete and Corroborated Prior Conception

The facts discussed above demonstrate that Dr. Ruben had a complete and corroborated conception prior to entry of Wiley into the field on June 29, 1995. The facts demonstrate that prior to Wiley's entry into the field, Dr. Ruben had conceived of a method for making an isolated antibody that specifically binds a polypeptide consisting of amino acids 1 to 281 of SEQ ID NO:2, which is subsection (a) of Proposed Count A. Dr. Ruben, in addition to having conceived of a method for making the subject matter of the count had predicted that the AIM-I protein would be useful in inducing apoptosis and in the treatment of cancer and that anti-AIM-I antibodies would be useful in treating autoimmune disease. Dr. Ruben's testimony as to his complete and operable conception is corroborated by, *inter alia*, the testimony of Ann Ferrie, Reiner Gentz, James Grinnell, Scott Conklin, and Alemseged Truneh, along with the Exhibits referred to in the testimony of Dr. Ruben and these corroborating witnesses.

B. Reduction to Practice

1. Legal Principles

a. Actual Reduction to Practice

Actual reduction to practice occurs when the inventor (a) made an embodiment or performed a process that meets every element of the interference count, and (b) demonstrated that the embodiment is capable of operating for its intended purpose. *Eaton v. Evans*, 204 F.3d 1094, 1097-98, 53 U.S.P.Q.2d 1696, 1698-99 (Fed. Cir. 2000).

The amount and nature of testing that an inventor must perform in order to show that an embodiment is capable of operating for its intended purpose "varies with the character of the invention and the problem it solves." *Scott v. Finney*, 34 F.3d 1058, 1062, 32 U.S.P.Q.2d 1115, 1119 (Fed. Cir. 1994). Testing to show actual reduction to practice does not require commercial perfection or absolute replication of the circumstances of the invention's ultimate use. *Id.*, 34 F.2d at 1063, 32 U.S.P.Q.2d at 1119.

An invention must be shown to "work for its intended purpose" to establish an actual reduction to practice. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327, 47 U.S.P.Q.2d 1896, 1901 (Fed. Cir. 1998). When the intended use of an invention is not specified in the count, however, a demonstration of substantial (or practical) utility for any purpose may be used to support a showing of actual reduction to practice. *See Nelson v. Bowler*, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (CCPA 1980); *Shurie v. Richmond*, 699 F.2d 1156, 1160, 216 U.S.P.Q. 1042, 1045 (Fed. Cir. 1983). Whether an asserted utility of an invention qualifies as a "substantial" or "practical" utility in an interference "must be decided on the basis of its own unique factual circumstances. Relevant evidence must be judged as a whole for its persuasiveness in determining whether the suggested use for the

compound of the count is a practical utility." *Cross v. Iizuka*, 753 F.2d 1040, 1048, 224 U.S.P.Q. 739, 745 (Fed. Cir. 1985).

As with conception and diligence, an inventor's testimony regarding activities directed to an actual reduction to practice must be corroborated. *See Woodland Trust v. Flowertree Nursery Inc.*, 148 F.3d 1368, 1371, 47 U.S.P.Q.2d 1363, 1365 (Fed. Cir. 1998). Independent corroboration may consist of "testimony of a witness, other than the inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor." *Reese v. Hurst*, 661 F.2d 1222, 1225, 211 U.S.P.Q. 936, 940 (CCPA 1981). Sufficiency of corroboration of activities relating to an actual reduction to practice is assessed under a "rule of reason." *Mann v. Werner*, 347 F.2d 636, 640, 146 U.S.P.Q. 199, 202 (CCPA 1965) ("The proper approach . . . involves a reasoned examination, analysis and evaluation of all the pertinent evidence bearing on the question, to the end that a reasoned determination as to the credibility of the inventor's story may be reached.")

b. Constructive Reduction to Practice

The filing of a patent application which discloses at least one species within the count in the manner required by 35 U.S.C. § 112, first paragraph constitutes a constructive reduction to practice. *Hyatt v. Boone*, 146 F.3d 1348, 1352, 47 U.S.P.Q.2d 1128, 1130 (Fed. Cir. 1998). A party need not have actually reduced the invention of the count to practice when relying on a constructive reduction to practice. *Yasuko Kawai v. Metlesics*, 480 F.2d 880, 885, 178 U.S.P.Q. 158, 162 (CCPA 1973).

2. Ruben's Actual Reduction to Practice

Dr. Ruben actually reduced the invention to practice by August 31, 1995, when Ms. Ferrie used anti-AIM-I antibodies to confirm by Western blot analysis that she obtained inducible AIM-I protein expression with the bacterial clone. RE158, ¶ 164.

3. Ruben's Constructive Reduction to Practice

On March 14, 1996, Dr. Ruben constructively reduced the invention to practice by filing provisional U.S. Patent Application No. 60/013,405 in the U.S. Patent & Trademark Office, to which the involved U. S. Patent Application 10/662,430, filed September 16, 2003, has been accorded benefit.

C. Diligence

Dr. Ruben was reasonably diligent from just prior to Wiley's earliest claimed priority date of June 29, 1995 until either (a) an actual reduction to practice by August 31, 1995 or (b) a constructive reduction to practice upon the filing of the '405 priority application on March 14, 1996.

1. Diligence Standard

One who is last to reduce to practice but first to conceive may establish priority by showing reasonable diligence extending from a time prior to the other party's conception to its own reduction to practice. 35 U.S.C. § 102(g) (2004); *In re Jolley*, 308 F.3d 1317, 1326, 64 U.S.P.Q.2d 1901, 1908 (Fed. Cir. 2002). Reasonable diligence does not require that a party work constantly on the invention to the exclusion of all other work. *Mycogen Plant Science, Inc. v. Monsanto Co.*, 252 F.3d 1306, 1316, 58 U.S.P.Q.2d 1891, 1899 (Fed. Cir. 2001). To prove diligence, however, a party must account for the entire ("critical") period from just prior to the other party's entry into the field up to the party's reduction to practice. *Griffith v. Kanamaru*, 816 F.2d 624, 626, 2

U.S.P.Q.2d 1361, 1362 (Fed. Cir. 1987). Reasonable diligence may be shown by either affirmative acts toward a reduction to practice or acceptable excuse or reasons for inactivity. *Hull v. Davenport*, 90 F.2d 103, 105, 33 U.S.P.Q. 506, 508 (CCPA 1937); *Griffith*, 816 F.2d at 626, 2 U.S.P.Q.2d at 1362.

Whether a party has exercised reasonable diligence must be considered in light of the particular circumstances of each case. *Price v. Symsek*, 988 F.2d 1187, 1196, 26 U.S.P.Q.2d 1031, 1038 (Fed. Cir. 1993); *Bey v. Kollonitsch*, 806 F.2d 1024, 1028 n.9, 231 U.S.P.Q. 967, 970 n.9 (Fed. Cir. 1986) ("the question of diligence is subject to the 'rule of reason' as determined in the particular circumstances of each case."); *Powell v. Poupitch*, 167 F.2d 514, 518, 77 U.S.P.Q. 379 (CCPA 1948).

To establish diligence, a party must provide specific details regarding dates and activities that took place during the critical period. *Kendall v. Searles*, 173 F.2d 986, 993, 81 U.S.P.Q.363, 369 (CCPA 1949). An inventor's testimony regarding his activity must be corroborated. *Jolley*, 308 F.3d at 1328, 64 U.S.P.Q.2d at 1909; *Gould v. Schawlow*, 363 F.2d 908, 919, 150 U.S.P.Q. 634, 643 (CCPA 1966); *Kendall*, 173 F.2d at 993, 81 U.S.P.Q. at 368-369. Corroboration, however, may be provided by sufficient independent circumstantial evidence, and corroboration of every factual issue contested by the parties is not required. *Jolley*, 308 F.3d at 1328, 64 U.S.P.Q.2d at 1909.

(a) Ongoing and Continuous Activities

Reasonable diligence does not require a showing of particular activity on each and every day of the critical period when evidence has been presented regarding experiments that were continuous and ongoing in nature covering the time period in question. *Monsanto Co. v. Mycogen Plant Science, Inc.*, 261 F.3d 1356, 1370, 59 U.S.P.Q.2d 1930, 1939 (Fed. Cir. 2001) (activities relating to the creation of Bt genes,

and activities relating to the tending and growing of plants, although not reflected by notebook entries on every day of the critical period, were sufficient to support a finding of diligence). Gaps in recorded activities may be reasonably explained by evidence suggesting that the work involved in the experiments was "ongoing without interruption, despite the lack of daily entries." *Id.*; *see also Jones v. Evans*, 46 F.2d 197, 202, 8 U.S.P.Q. 240, 245 (CCPA 1931).

(b) Tacking Activities Relating to an Actual Reduction to Practice Onto Activities Relating to a Constructive Reduction to Practice

Diligence may be established by "tacking" prior activity toward an actual reduction to practice (e.g., experimentation or testing a working embodiment) onto later activity toward constructive reduction to practice (e.g., the preparation and filing of a patent application). *Rey-Bellet v. Englehardt*, 493 F.2d 1380, 1387-88, 181 U.S.P.Q. 453, 458 (CCPA 1974).

(c) Attorney Diligence

In assessing attorney diligence toward constructive reduction to practice, it is not necessary for the attorney to focus exclusively on the application at issue; when there is a backlog of work, it is sufficient that the application be taken up in a chronological and expeditious manner. *Rines v. Morgan*, 250 F.2d 365, 369, 116 U.S.P.Q. 145, 148 (CCPA 1957); *Bey*, 806 F.2d at 1029, 231 U.S.P.Q. at 970.

(d) Activities by Non-Inventors

It is not necessary for the inventor to personally reduce his invention to practice; "activities by others working explicitly or implicitly at the inventor's request will inure to his benefit." *Cooper v. Goldfarb*, 154 F.3d 1321, 1332, 47 U.S.P.Q.2d 1898, 1905 (Fed. Cir. 1998) (quoting 3 Donald S. Chisum, Chisum on Patents § 10.06[3] (1995));

Burroughs Wellcome Co. v. Barr Lab., Inc., 40 F.3d 1223, 1230, 32 U.S.P.Q.2d 1915, 1921-22 (Fed. Cir. 1994) (testing of AZT by scientists at the National Institutes of Health inures to the benefit of the pharmaceutical manufacturer that conceived of the invention); *Gianladis v. Kass*, 324 F.2d 322, 328, 139 U.S.P.Q. 300, 305 (CCPA 1963) (attorney's efforts inure to the benefit of the inventor in establishing diligence). Moreover, a non-inventor's confirmation of the utility of an invention can inure to the benefit of an inventor if: (1) the inventor conceived of the invention, (2) the inventor had an expectation that the embodiment being tested would work for the intended purpose of the invention; and (3) the inventor submitted the embodiment for testing for the intended purpose of the invention. *Genentech, Inc. v. Chiron Corp.*, 220 F.3d 1345, 1354, 55 U.S.P.Q.2d 1636, 1643 (Fed. Cir. 2000).

2. Ruben's Diligence

a. Activities During The Critical Period

The activities documented below and set forth on the accompanying timeline of activities (RE12), and on the day-to-day calendar of activities (RE11), demonstrate that Dr. Ruben worked with reasonable diligence toward reducing to practice the subject matter of the count from a time just prior to June 29, 1995 until Dr. Ruben's reductions to practice ("the critical period").

As was explained by Dr. Ruben, and corroborated by Dr. Gentz, HGS's program for high priority projects involved a variety of discovery platforms, as illustrated schematically in RE15, that were utilized in tandem and in mutual dependence to obtain information about AIM-I and to guide the development of AIM-I-related therapeutics such as anti-AIM-I antibodies encompassed by the proposed count A. RE157, ¶¶ 15-21. RE58, ¶¶ 2, 5. In the 1995-96 time period, HGS was still a new start-up company

(founded in 1992) that was not only cloning many new genes, but also developing the infrastructure to screen and characterize these new genes. RE157, ¶¶ 15-21. RE58, ¶¶ 2, 5. HGS's organized research plan for the development of AIM-I included the following activities: (a) identifying and establishing suitable systems and conditions for expression of AIM-I and thus for the development of AIM-I-related therapeutics; (b) AIM-I antibody production; (c) Western blotting of AIM-I protein; (d) performing Northern blots analyses to assess the tissue and cell specificity (e.g., cancer cells, immune cells) of expression of the AIM-I gene; and (e) analyzing by immunofluorescence AIM-I expression in cells. RE158. RE157. The cloning and sequence revision of AIM-I cDNA, coupled with the recognition by Dr. Ruben that AIM-I is a novel member of a small group of apoptosis-inducing TNF ligands, provided the motivation to 1) produce AIM-I protein and antibodies (Production Activities), and 2) to further characterize the expression, chromosomal location, and cellular localization of AIM-I (Characterization Activities). RE15. As indicated in RE15, the Production Activities and Characterization Activities complemented each other. For example, conducting Western blots to detect AIM-I expression required the production of antibodies against AIM-I, which in turn required the successful expression of AIM-I protein from the isolated DNA. All of these research platforms contributed information that advanced the development of AIM-I based therapeutics, as described in more detail below.

i. AIM-I Expression Constructs

(a) Insect Cell Expression of AIM-I

As part of their research and development program, Dr. Ruben and his colleagues sought to identify appropriate systems in which to produce the AIM-I protein from the nucleic acid that Dr. Ruben had isolated, to be used, *e.g.*, for the production of

antibodies. Insect cell expression systems generally provide for proper post-translational processing of proteins (*e.g.*, glycosylation) and thus are an attractive platform for the development of a therapeutic protein that could be used to treat cancer or raise an antibody to treat autoimmune disease. RE157, ¶ 26.

At the direction of Dr. Ruben and beginning on September 2, 1994, Ms. Ferrie constructed a baculovirus expression vector for expression of AIM-I in insect cells, and such expression experiments were carried out by the Protein Expression Department of HGS. RE158, ¶¶ 21-47. The vector was prepared by Ms. Ferrie from the baculovirus vector pA2 and contained an isolated polynucleotide encoding amino acids 1-281 of SEQ ID NO:2 (i.e., full-length AIM-I, also known as "Met-1" or "HTPAN08SO4-51bp"). RE158, ¶¶ 21-22. Ms. Ferrie's work relating to insect cell expression of AIM-I began at least by September 2, 1994 and continued at least until February 15, 1995, when she submitted the baculovirus clone for sequencing to the Protein Expression Department at HGS for recombinant baculovirus production. RE158, ¶ 47.

Beginning at least by February 17, 1995 and continuing at least through May 9, 1995, Solange Gentz worked to plaque purify baculovirus containing a nucleic acid encoding the Met-1 form of AIM-I (HTPAN08SO4-51bp). RE68, ¶¶ 2-15.

Beginning at least by June 12, 1995 and continuing at least through June 23, 1995, Timothy Coleman worked to assess the recombinant expression of AIM-I protein from the above-described baculoviral vector in Sf9 insect cells. RE64, ¶¶ 5-9. Specifically, Dr. Coleman carried out pulse-labeling of the protein expressed in the Sf9 insect cells. RE64, ¶ 5.

The activities of Ms. Ferrie, Ms. Gentz, and Dr. Coleman inure to the benefit of Dr. Ruben in establishing diligence as each of them worked at Dr. Ruben's direction.

Cooper, 154 F.3d at 1332, 47 U.S.P.Q.2d at 1905. Moreover, the testimony of each of Ms. Ferrie, Ms. Gentz, and Dr. Coleman corroborates Dr. Ruben's testimony relating to his diligence in reducing the invention to practice.

(b) Bacterial Cell Expression and Purification of AIM-I

In addition to the insect cell expression system, Dr. Ruben and his colleagues explored the use of bacterial expression systems for producing AIM-I to be used for the production of antibodies for analyzing the expression patterns and function of the protein and for developing the antibodies as therapeutic reagents. RE157, ¶ 23. Prior to June 29, 1995, Dr. Ruben had directed Ms. Ferrie to clone the full-length AIM-I coding sequence into the bacterial expression vectors pD10 and pQE60. RE158, ¶¶ 48, 90. Ms. Ferrie then expressed AIM-I in bacteria and purified it by $NiSO_4$ chromatography and by preparative gel electrophoresis. RE158, ¶ 158.

More specifically, on June 27, 1995, Ms. Ferrie worked under the direction of Dr. Ruben to grow a culture of bacteria that had been engineered to express the full-length AIM-I polypeptide (also known as HTPAN08SO4 51bp ATG +pD10). RE158, ¶ 161. She then subjected the expressed protein to polyacrylamide gel electrophoresis (PAGE) and purified the protein by column chromatography on June 28-30, 1995. RE158, ¶ 163. By at least August 30, 1995 and continuing during each subsequent month through December 1995, and again in February and March of 1996, Ms. Ferrie further worked to (i) subclone the AIM-I DNA into suitable genetic constructs for expression in bacteria, (ii) express AIM-I in bacteria and to characterize the expressed protein by PAGE and/or Western blot analysis (further discussed below), (iii) purify the expressed AIM-I protein by column chromatography or PAGE, and (iv) produce antibodies against AIM-I.

RE158, ¶¶ 155-202. Thus, these activities reveal that Ms. Ferrie worked diligently at the direction of Dr. Ruben to develop an appropriate expression system for using the AIM-I polynucleotide to produce AIM-I protein during the critical period which could be further used to produce anti-AIM-I antibodies for analyzing the expression patterns and activity of the protein, as well as conforming its production through recombinant constructs, and for developing the antibodies as therapeutic reagents. Ms. Ferrie's efforts inure to the benefit of Dr. Ruben and corroborate his testimony that he exercised reasonable diligence in seeking to reduce to practice the subject matter of the count. *Cooper*, 154 F.3d at 1332, 47 U.S.P.Q.2d at 1905.

(c) *In Vitro* Expression of AIM-I

Dr. Ruben also explored the use of an *in vitro* expression system for producing AIM-I protein from the mRNA transcripts of AIM-I. Working under the direction of Dr. Ruben, Ms. Ferrie worked to express AIM-I *in vitro* in a rabbit reticulocyte lysate expression system known as "TNT." RE158, ¶¶ 109-10 and 115-16. Such experiments initially were carried out in August 1994 and January of 1995. RE145, ¶ 2 and RE158, ¶¶ 109-10. Additional experiments were carried out by Ms. Ferrie on December 20, 1995 and January 26, 1996. RE158, ¶¶ 115-16.

The use of a rabbit reticulocyte lysate expression system provides a means for determining whether a correct cDNA construct has been assembled and isolated, ensuring that the genetic construct employed encodes viable translation initiation and termination signals, *i.e.*, confirming that the gene is expressible. RE157, ¶ 27. RE158, ¶ 8. Ms. Ferrie's successful use of this *in vitro* protein expression system inures to the benefit of Dr. Ruben, as she worked at his direction to test the isolated nucleic acid that he was going to use to produce antigen that would then be used to produce anti-AIM-I

antibodies. *Cooper*, 154 F.3d at 1332, 47 U.S.P.Q.2d at 1905. Additionally, Ms. Ferrie's testimony corroborates the testimony of Dr. Ruben that he sought to use reasonable diligence toward reducing the invention to practice by, *inter alia*, expressing AIM-I protein *in vitro*.

ii. AIM-I Antibody Production

Ann Ferrie (f.k.a. Ann M. Kim) sent a sample of purified AIM-I protein to Pocono Farm for antisera production on June 26, 1995. RE158, ¶ 160. On June 30, 1995, Pocono Farm began a six-month period of continuous activity on behalf of Ruben for production of AIM-I antisera, under the supervision of Scott Conklin. A synopsis of Pocono Farm activities is set forth below, and a detailed account is provided in the attached Conklin Declaration. RE18.

iii. Activities at Pocono Farm

As evidenced by the Declaration of Scott Conklin referred to previously (RE18), a period of continuous activity occurred at the Pocono Rabbit Farm & Laboratory ("Pocono Farm") for the production of anti-AIM-I polyclonal antisera which inures to Ruben's benefit. Specifically, Mr. Conklin avers that he personally supervised the raising of the anti-AIM-I antibodies, which correspond to the proposed count, that were used in Ann Ferrie's experiments described herein. RE18, ¶ 4. Mr. Conklin also mentions the agreement between HGS and Pocono Farm which was generally followed for the production of antisera in over one hundred projects since July, 1993. RE18, ¶ 2. Mr. Conklin describes laboratory records for rabbits 11940 and 11941 which were immunized with AIM-I protein (referred to as "FasLig") received from Ann Ferrie on or before June 30, 1995. RE18, ¶ 4.

Mr. Conklin has provided and explained the Health Cards and an electronic record of the bleeds of rabbits 11940 and 11941. RE8, ¶ 4. The evidence demonstrates that both rabbit 11940 and 11941 were maintained for continuous antiserum production from at least June 30, 1995 to at least January 2, 1996. The isolated antibodies from each rabbit were sent to HGS on January 3, 1996 for use in studying the expression patterns and activity of the AIM-I protein.. Mr. Conklin has detailed specific steps of the protocol used for the AIM-I rabbits in paragraph 4 of his declaration. Mr. Conklin avers that, once a project is initiated, a schedule of immunization and care is triggered which proceeds along a continuous time course dictated by the rabbit's biology which, for AIM-I, lasted about six months. RE18.

iv. Western Blot Analysis (Actual Reduction to Practice on August 31, 1995) and Antibody Production at SmithKline Beecham

Ms. Ferrie used the isolated antibodies directed against AIM-I in Western blot analyses of AIM-I protein expression in bacteria that she had engineered to produce AIM-I. RE158, ¶ 162. More specifically, on August 31, 1995, Ms. Ferrie used the antibodies to confirm by Western blot analysis that she obtained inducible AIM-I protein expression with the bacterial clone "HTPAN08SO4 51bp ATG +pD10," which she had engineered to contain a polynucleotide encoding amino acids 1-281 of SEQ ID NO:2. RE158, ¶ 164. In the August 31, 1995 experiment, Ms. Ferrie, working under the direction of Dr. Ruben, compared the Western blot results obtained with isolated antibodies obtained from rabbits prior to inoculation with the AIM-I antigen ("pre-bleed sera") versus sera obtained from rabbits after inoculation with the AIM-I antigen ("test bleed sera"). Ms. Ferrie stated that the Western blot "showed a positive result in the induced protein lane using test bleed sera but not pre-bleed sera. This result indicated

the binding of antibody to the AIM-I protein expressed from the HTPAN08S04 51bp ATG bacterial expression construct and confirmed the presence of antibodies specific for AIM-I in the initial, small antisera samples." RE158, ¶ 164.

Thus, by August 31, 1995, Dr. Ruben had directed the making, using, and testing of an isolated antibody that specifically binds a protein consisting of amino acids 1 to 281 of SEQ ID NO:2. As demonstrated by the aforementioned experiment, the polynucleotide was expressed in bacteria to produce AIM-I protein against which antibodies were raised and later used in detecting AIM-I expression in an inducible expression system. As discussed by Dr. Ruben, antibody production was part of a protocol in place at HGS for characterizing and developing molecules of high therapeutic interest. RE157, ¶ 23. Moreover, by August 31, 1995, Dr. Ruben had used the antibodies directed against AIM-I in the characterization of inducible expression of AIM-I protein, RE158, ¶ 164. When, as here, the intended use of an invention is not specified in the count, a demonstration of a substantial or practical utility for any purpose may be used to support a showing of actual reduction to practice. *Nelson*, 626 F.2d at 1160, 206 U.S.P.Q.2d at 883; *see also Rey-Bellet*, 493 F.2d at 1383, 181 U.S.P.Q. at 454 (Since the count contains no limitation related to any utility, evidence which would establish a substantial utility for any purpose is sufficient to show its reduction to practice). The use of the antibodies in characterizing the inducible expression of AIM-I protein constitutes such a substantial or practical utility.

Additional antibody production was carried out by Dr. Ruben's collaborators at SmithKline Beecham ("SB"), and is described in the testimony of Mr. Edward Dul. RE30, ¶ 4. As Mr. Dul testified, the AIM-I protein was injected into a rabbit maintained by SB on or about November 1, 1995, and the rabbit was maintained at least until May 1,

1996, during which time it produced antisera against AIM-I (termed "CK9B" antisera). RE30, ¶ 4. Antibodies produced from the rabbit were used, *inter alia*, in Western blot analysis of recombinantly-produced AIM-I protein. RE59, ¶ 8. As Dr. Truneh testified, the production of antibodies and their use in Western blot analysis were part of a "critical path" strategy undertaken by the HGS/SB joint venture for analyzing TNF-related genes. RE59, ¶ 8. Thus, the work of Dr. Ruben's collaborators at SB inures to the benefit of Dr. Ruben in establishing diligence toward reducing the invention to practice.

v. Indirect Immunofluorescence

Under Dr. Ruben's supervision, Ms. Ferrie carried out indirect immunofluorescence analysis of the AIM-I protein as part of their overall effort to obtain a detailed understanding of the biological properties of AIM-I as they exist in a living mammalian cell. RE158, ¶¶ 203-208. RE157, ¶¶ 20, 30. Generally, immunocytochemistry can be used to reveal the subcellular localization of a protein. Moreover, a protein under study can be genetically engineered to display antigen tags at various locations along the linear sequence of the protein, such as at the N-terminus and the C-terminus. The tagged protein can then be subjected to immunocytochemical analysis to reveal the subcellular localization of specific antigen-tagged portions of the protein. Such an approach can reveal important information about protein processing, topology, and orientation within cellular membranes which relates to the overall development of AIM-I therapeutics. Ms. Ferrie's immunofluorescence experiments were designed to determine the subcellular location of the AIM-I protein. Ms. Ferrie avers to the specific activities associated with AIM-I immunofluorescence beginning on September 25, 1995. RE158, ¶¶ 203-208. Ms. Ferrie's testimony corroborates the testimony and diligence of Dr. Ruben. RE158, ¶¶ 203-08.

vi. Northern Blot Analysis

Dr. Ruben also sought to determine the tissue specificity and cell specificity of expression of the AIM-I gene by Northern blot analysis. RE157, ¶ 19. This information, for example, whether or not AIM-I is expressed in cancer cells and immune system cells, is useful in confirming therapeutic and diagnostic applications of AIM-I protein and AIM-I antibodies, and in developing animal models and test protocols when assessing AIM-I therapeutics. RE157, ¶ 19. Therefore, beginning by at least December 7, 1995 and continuing at least until December 11, 1995, Ms. Ferrie worked under the direction of Dr. Ruben to carry out Northern blot analysis and to determine the tissue expression profile of AIM-I. RE158, ¶¶ 210-212. Thus, Ms. Ferrie's testimony corroborates Dr. Ruben's acts of diligence towards reducing the invention to practice.

Dr. Ruben also collaborated with scientists at SB in conducting Northern blot analyses of AIM-I expression. Beginning at least by August 16, 1995, and continuing at least until October 18, 1995, Kong Tan of SB conducted a series of Northern blot experiments to detect AIM-I expression in a wide variety of cell types. RE25, ¶¶ 2-6.

By October 18, 1995, Mr. Tan had performed at least four Northern blot analyses of AIM-I expression in various tissues, immune cells, and leukemia cell lines (e.g., Jurkat cells, brain, heart, lung, thymus, spleen, liver, kidney, small intestine, prostate, etc). RE25, ¶¶ 2-6. Mr. Tan then reported the tissue and cell specificity of AIM-I expression to his colleagues at an October 18, 1995 meeting between collaborators from SB and HGS. RE25, ¶ 6. Although Dr. Ruben did not attend that meeting of the HGS/SB joint venture, he reviewed the meeting notes shortly thereafter. The meeting notes indicate that Northern blot analysis was successfully used to determine the cell and tissue specificity of AIM-I expression. RE25, ¶ 6. RE71. Particularly, the Northern

data showed that AIM-I was highly expressed in activated CD4+ T cells. RE77, page 5, Table 2, column 3, row 16. At this time, Fas ligand, which shares a high degree of sequence homology with AIM-I, was known to be expressed in activated CD4+ T cells and known to induce apoptosis, further substantiating Dr. Ruben's conception that AIM-I would also be involved in inducing apoptosis and anti-AIM-I antibodies would be useful in treating autoimmune diseases. RE113, pg.914, right col. ¶ 2.

vii. Chromosomal Mapping

Dr. Ruben instructed the HGS chromosomal mapping core facility to determine the chromosomal location of the AIM-I gene in December 1995 to determine whether the gene mapped close to any known disease-associated genes and to further elucidate the biological role of AIM-I and its value as a therapeutic or diagnostic agent. RE157, ¶¶ 34-37. The AIM-I gene was determined to specifically map to chromosome 3q25-27 on December 5, 1995. RE157, ¶ 37.

On November 29, 1995, Dr. Ruben made an internal HGS request for chromosomal mapping of the AIM-I gene, as indicated on the standard HGS order form DNA Probe for Chromosomal Mapping Request #279 order form, dated November 29, 1995. RE157, ¶ 35. As shown on the HGS order form, the probe was to be prepared from the HTPAN08SO4 clone (*i.e.*, from the nucleotide sequence encoding full-length AIM-I). RE157, ¶ 35. Dr. Ruben made this request for the intended purpose of mapping the AIM-I gene and he expected the clone to map to a specific position in the human genome. RE157, ¶ 35.

On November 30, 1995, an AIM-I nucleic acid probe was labeled for the chromosomal mapping procedure by Meena Augustus, who was a chromosomal mapping technician in the HGS Exploratory Research department supervised by Ken

Carter at that time. RE157, ¶ 36. As shown in Ms. Augustus's laboratory notebooks, which were authenticated by Michele Wales, she prepared a probe by "nick translating" HTPAN08SO4, next to which she had noted "Steve Fas Ligand." RE104, page 97.

On December 5, 1995, AIM-I was determined to map to chromosome 3q25-27. RE157, ¶ 37. The chromosomal mapping results are set forth in Ms. Augustus's laboratory notebook, which indicates that the "Gene Name: FAS-Ligand HTPAN08SO4" for "Scientist: Steve Ruben" had a "band position: 3q25-27." RE104, page 101. On December 6, 1995, the mapping information was entered into the IRIS database. RE157, ¶ 37. RE104, page 101. The result of the mapping experiment was communicated to Dr. Ruben by either Ken Carter or one of his assistants within two to three days of December 5, 1995. RE157, ¶ 37. Additionally, the determination of the chromosomal location of the AIM-I gene to 3q25-27, a region known to be rearranged in diseases such as cancer, confirms that the isolated nucleic acid corresponds to a specific gene in the human genome.

Dr. Ruben's testimony is corroborated by the contemporaneously-produced laboratory notebook records of Meena Augustus, which were authenticated by Michele Wales. RE104, pages 97-101. RE141. As Meena Augustus worked at the request of Dr. Ruben, Ms. Augustus' activities inure to the benefit of Dr. Ruben and corroborate Dr. Ruben's assertion that he diligently sought to reduce to practice the invention. *Cooper*, 154 F.3d at 1321, 47 U.S.P.Q.2d at 1905.

viii. Activities of the HGS/SB Joint Program

Activities were ongoing from just prior to June 29, 1995 until at least March 14, 1996 among a large group of scientists participating in a joint collaboration of HGS and SB designed to identify and characterize members of the TNF ligand and TNF receptor

families (the "Joint Program"). Though these activities are not necessary to meet our burden under 37 C.F.R. § 41.202(d), they have been included to complete the record.

It was known at the time of the joint HGS/SB meeting concerning the TNF/TNFR family on October 18, 1995 that the TNF family of ligands, including AIM-I, was involved in a complex system of regulation of immune cell proliferation and activity effected through the binding of each ligand to one or more TNF receptor family members. To better understand the role and mechanism of TNF/TNFR family ligand-receptor interactions, including AIM-I apoptotic activity, it was important to identify as many TNF ligand and receptor family members as possible. Also important for analysis of AIM-I function was an assessment of RNA expression patterns among various members of the TNF ligand and TNF receptor families. RE59.

The activities of the HGS/SB Joint Program described in this section contribute to Dr. Ruben's diligence under the principle of inurement. The October 18, 1995 HGS/SB meeting minutes, supporting materials, and activities leading up to the meeting provide a detailed overview of the tremendous amount of activity being jointly conducted by HGS and SB in order to elucidate and understand the structure and function of AIM-I and related ligands, receptors, and receptor-associated proteins comprising the TNF/TNFR cell signal transduction network. *See* RE59 and exhibits thereto. Although Dr. Ruben did not attend that meeting of the HGS/SB joint collaboration, he reviewed the meeting notes shortly thereafter.

Alem Truneh is employed by GlaxoSmithKline (formerly SmithKline Beecham) and acted in a scientific and management role for SB during the critical period. RE59, ¶ 1. Dr. Truneh avers that work relating to AIM-I was being conducted by, at least, Reiner Gentz, Jian Ni, Guo-Liang Yu, each of HGS, and himself, Kong B. Tan, Edward R.

Appelbaum, and Edward Dul, each of SB, and still others at SB at that time. RE59, ¶ 4. As early as July l, 1994, Peter R. Young of SB submitted a request for full sequencing of AIM-I. RE59, ¶5. Dr. Truneh avers that the results of the July 1, 1994 sequencing request by Mr. Young corroborated the full-length AIM-I sequence determined by Dr. Ruben. RE59, ¶ 5.

Dr. Truneh refers to a number of internal SB e-mails beginning March 13, 1995 which memorialize activities that were ongoing at SB in connection with AIM-I prior to the October 18, 1995 meeting. RE59, ¶ 6. Dr. Truneh describes his efforts to coordinate an agenda for the October 18, 1995 meeting. RE59, ¶ 7. Topics included updates on progress relating to (a) sequence analysis, (b) potential TNF receptors and ligands in the HGS database, (c) tissue and cell distribution of novel TNF/TNFR-related genes, (d) expression of soluble ligands, (e) construction and expression of Ig-fusion proteins of TNFR homologs and plans for making antibodies, (f) biological activity of novel TNF/TNFR molecules, and (g) the cloning of Fas and Fas ligand. RE59, ¶ 7. The working party distribution list for the October 18, 1995 meeting minutes included 33 individuals at SB and four individuals at HGS, emphasizing the scope and importance of this event and the underlying activities to both companies. In actual attendance at the meeting were 17 individuals from SB and three individuals from HGS. RE59, ¶ 7.

Dr. Truneh attended the October 18, 1995 meeting, and avers to the meeting minutes attached to his declaration, and to Peter Young's presentation of the group's overall strategy for identification of gene function for TNF/TNFR related genes. RE59, ¶ 8. Dr. Truneh describes meeting presentations by Kong Tan and Edward Dul regarding various aspects of AIM-I studies (see these respective declarations referred to below). RE59, ¶¶ 13-15.

Dr. Truneh avers to Joint Program activities subsequent to the October 18, 1995 meeting, including preparation of a monthly report for Gordon Moore of SB, and additional internal SB e-mail messages. RE59, ¶¶ 16-17. Dr. Truneh avers that, in view of his document review and his personal involvement in the HGS/SB Joint Program, he believes that activities relating to AIM-I were virtually continuous throughout the critical period from just prior to June 29, 1995 until March 14, 1996.

Kong B. Tan, Ph.D., a Senior Scientist at SB, conducted a series of RNA blot ("Northern analysis") experiments in collaboration with Dr. Ruben to reveal and compare expression patterns of AIM-I and other novel TNF/TNFR family members. *See* RE25, ¶ 2. Dr. Tan performed at least four Northern analyses relating to AIM-I prior to the October 18, 1995 meeting, beginning in August 1995. RE25, ¶¶ 2-5. Dr. Tan's experiments probed AIM-I expression in a variety of tissues and cell lines, including brain, heart, lung, thymus, spleen, liver, kidney, small intestine, prostate, MG63, TF274, KG1a, KG1, NL60, THP1 CD19+, CD4+, BM105, MCF7, Molt 3, Raji, Raji HN2, REH, CD8+, Jurkat, HL60, U937, THPI, KG1a and PLB. RE25, ¶¶ 2-5. Dr. Tan presented the results of these analyses at the October 18, 1995 meeting, and provided RNA expression summary tables for inclusion in the meeting minutes. RE25, ¶ 6.

Edward Dul acted in a scientific role for SB during the critical period. RE30, ¶ 1. Mr. Dul performed Western analysis of the AIM-I protein in the weeks leading up to the October 18, 1995 meeting and thereafter under the supervision of SB scientist Edward R. Appelbaum, in collaboration with Dr. Ruben. RE30, ¶ 2. Mr. Dul's objectives were to express AIM-I as a fusion protein in *E. coli* for use in raising antibodies and to express AIM-I in soluble form in *E. coli* or other systems for use in receptor binding and activity assays. RE30, ¶ 2. Mr. Dul describes his preparation of AIM-I fusion protein constructs

and work directed to AIM-I expression and Western blotting that he did beginning about July 11, 1995. RE30, ¶ 3. For example, Mr. Dul imaged a coomassie-stained protein gel on December 14, 1995 and described a Western blot which showed recognition of AIM-I ("purified TL2") with antisera raised at SB (the "CK913" antisera) and with antisera obtained from HGS. RE30, ¶ 4. Mr. Dul avers that work on AIM-I antisera production began at SB on or about November 1, 1995 and continued at least until about May 1, 1996. RE30, ¶ 4. Mr. Dul's experiments using bleed 3 of AIM-I antisera CK9B, various AIM-I expression constructs, and various induction temperatures in connection with AIM-I solubility studies were performed in early March, 1996. RE30, ¶ 6.

Reiner L Gentz, Ph.D., was employed by HGS as Senior Vice President, Protein Development. RE58, ¶ 1. During the critical period, Dr. Gentz was employed as Director, Protein Expression and Purification, and managed the HGS/SB Joint Program, which included his attending meetings with SB personnel and internal HGS meetings, as well as corresponding with SB personnel. Dr. Gentz avers to the role of Dr. Guo-Lung Yu and Lilly Xing, members of the Joint Program, in connection with Yu's and Xing's activities respecting AIM-I during the critical period. RE58, ¶¶ 6-40.

Dr. Gentz avers that Dr. Yu both directly performed experiments and supervised Lily Xing in her performance of experiments analyzing members of the TNF ligand family, including AIM-I. Dr. Gentz describes the HGS procedure for signing and witnessing notebooks in place at that time, and further avers that, after reviewing Dr. Yu's laboratory notebooks and based on Dr. Gentz' personal knowledge of Dr. Yu's research at that time, Dr. Yu in fact carried out the activities particularized in the Gentz declaration beginning August 21, 1995 and continuing at least until March 13, 1996. RE58, ¶¶ 7-8. Briefly, Dr. Yu performed experiments involving several TNF ligands

including AIM-I, TNF gamma, TNF delta and TNF epsilon, and at least one TNF receptor having a death domain. RE11.

Dr. Gentz avers that Lilly Xing was employed by HGS as a Research Associate in the Department of Molecular Biology under the direct supervision of Dr. Yu during the critical period. RE58, ¶ 32. Dr. Gentz avers that, after reviewing Ms. Xing's laboratory notebook and based on Dr. Gentz' personal knowledge of Ms. Xing's research at that time, Ms. Xing in fact carried out the activities particularized in the Gentz declaration beginning in February 1996 and continuing until the middle of March 1996. RE58, ¶ 33. Briefly, Ms. Xing performed experiments analyzing members of the TNF ligand family, including AIM-I. RE58, ¶¶ 35-40.

Solange Gentz (formerly Solange H. Lima) worked as a Research Associate at HGS in the Department of Protein Development during the critical period under the direct supervision of Dr. Timothy Coleman. RE68, ¶ 1. Prior to June 1995, Ms. Lima had carried out a large number of experiments to engineer and express AIM-I in insect cells using the baculovirus expression system. RE68. ¶¶ 4-16. During the critical period, she amplified a transfected CHO dhfr- cell line producing TNF gamma with methotrexate (MTX). These activities are described with particularity in her declaration. RE68, ¶¶ 17-47. Briefly, Ms. Lima initiated the TNF gamma amplification process on October 3, 1995, and pursued it continuously until December 12, 1995. RE68, ¶¶ 17-29. After a brief reprieve, spanning holiday and weather-related closures at HGS (*see* Ferrie Declaration, RE158, ¶ 214.), Ms. Lima performed a continuous cell culture treatment from January 22, 1996 until March 13, 1996. RE68, ¶¶ 30-47. The amplification was for the purpose of increasing the expression level of the recombinant TNF gamma protein for functional studies. Ms. Lima also prepared a baculovirus vector containing a

soluble TNF receptor family member (clone HTOAU65) for expression in insect cells. RE68, ¶ 36.

Timothy A. Coleman, Ph.D., was employed by HGS from March 1993 to November 2001. During the time period discussed below, he held the position of Scientist in the HGS Protein Expression and Purification Department, working under the supervision of Dr. Reiner Gentz in collaboration with Dr. Ruben. RE64, ¶ 1. Dr. Coleman and Solange Gentz initiated work to express the AIM-I protein in insect cells. These activities are described with particularity in his declaration. RE64. Briefly, on June 12, 1995, Dr. Tim Coleman began a pulse-labeling experiment to assess the recombinant expression of AIM-I protein from expression constructs obtained from Ms. Gentz. RE64, ¶ 3. Dr. Coleman referred to these constructs in his notebook as FAS-51 and FAS-185 (clones HTPAN08S04-51 bp and HTPAN08S04-185 bp, respectively). RE64, ¶ 3. For each construct, Dr. Coleman tested two viral isolates (referred to in his notebook as -1 and -2). RE64, ¶ 5. RE65, pages 110-11. The viral infection of Sf9 cells was followed by removing the growth media and adding a serum-free medium containing ^{35}S-methionine and ^{35}S-cysteine. The label was allowed to incorporate overnight, and then supernatant and cell extracts were prepared for SDS-PAGE analysis. Thus, in the experiments Dr. Coleman initiated on June 12, 1995, the infections and labeling would represent continuous work through at least June 16, 1995. RE64, ¶ 6.

On June 16, 1995, Dr. Coleman ran SDS-PAGE gels of extracts of the pulse-labeled Sf9 cells (including cells infected with the viruses harboring the AIM-I constructs and the wild type virus control) and allowed the gels to dry overnight, i.e., until June 17, 1995. RE64, ¶ 7. The dried gel was subjected to autoradiography for different periods of time to visualize the labeled protein bands; a 42 hour exposure and a

100 hour exposure. RE64, ¶ 8. RE66. The 42 hour exposure began on June 17, 1995 and was developed on June 19, 1995. RE64, ¶ 8. The 100 hour exposure was likely initiated on June 19, 1995 and developed on June 23, 1995. RE64, ¶ 8. The autoradiogram of the 100-hour exposure indicates an approximately 31 kilodalton band present in the lane corresponding to the FAS-185-expressing cells, which is approximately the predicted molecular weight of the protein encoded by this construct. This band is absent from the apparently uninfected Sf9 cells. RE64, ¶ 9. RE66.

Since 1994, Markus Buergin has worked as a Research Associate at HGS in the Department of Protein Development. RE54, ¶ 1. Mr. Buergin performed experiments during the critical period to produce stable cell lines containing recombinant constructs prepared by Guo-Liang Yu encoding TNF delta (HLTBT71) for the purpose of producing recombinant TNF delta protein for further analysis of its biological properties. RE54, ¶ 2. Mr. Buergin avers that his procedure for producing the stable recombinant cell lines was a continuous, uninterrupted one from the time of transfection on November 29, 1995 through March 14, 1996. RE54, ¶ 3. Mr. Buergin describes with particularity the activities he performed during the procedure in his attached declaration. RE54.

ix. Activities of Patent Counsel

The following brief synopsis relates to the preparation and filing of the AIM-I '406 priority application. The activities mentioned are explained in greater detail in the declarations of Ms. Beckman and Mr. Olstein referred to below.

On January 29, 1996, Robert Benson, Ph.D., Esq., then head of the HGS Legal Department, received a letter from Edward R. Gimmi, Ph.D., Esq. of SB, inquiring about the filing of a patent application for AIM-I. Two days later, Kathryn L. Beckman, then Intellectual Property Administrator at HGS, mailed the AIM-I disclosure and related

references to Gregory D. Ferraro, Esq. of Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein ("Carella"), then outside patent counsel for HGS, requesting that a patent application be prepared for filing on an expedited basis. RE33, ¶ 2. Mr. Ferraro mailed a draft application to Benson and Gimmi for review on February 2, 1996. RE33, ¶ 5.

Ann Ferrie aliquoted AIM-I DNA for deposit with the ATCC® on February 12, 1996. RE95, page 16. On February 16, 1996, Benson executed a form for the ATCC® deposit and Tina Powers of HGS completed a corresponding purchase order. ATCC® received the deposit and assigned it Accession No. 97448 on February 20, 1996, and tested the viability of the deposited culture a few days later. On February 27, 1996, the HGS Legal Department received evidence from ATCC® that the deposit had, in fact, been made and tested for viability. On March 4, 5, 8, 13 and 14, 1996, Charles J. Herron of Carella worked on the AIM-I application. Mr. Herron filed two applications having an identical disclosure, i.e. Provisional Application No. 60/013,405 and PCT/US96/03773 designating all states including the United States. Accordingly, a constructive reduction to practice of the subject matter of RUBEN PROPOSED COUNT A was established on March 14, 1996.

A Declaration of Kathryn L. Beckman avers to HGS Legal Department activities in connection with the AIM-I patent application which occurred in January through March 1996. RE33. Ms. Beckman was Intellectual Property Administrator at HGS from February 1995 until June 1998, reporting directly to Mr. Benson. RE33, ¶ 1. Ms. Beckman's responsibilities included establishing and supervising a patent application docketing system, corresponding with outside patent counsel, and corresponding with HGS scientists in preparation of patent applications. RE33, ¶ 1. Ms. Beckman's declaration explains activities respecting the AIM-I application, including her January

31, 1996 instructions to Mr. Ferraro of Carella to "give the PF261 application priority over all other applications you are currently handling for HGS in order that it may be drafted and filed on an expedited basis." RE33, ¶ 2. Mr. Ferraro's draft arrived on February 5, 1996, and Ms. Beckman docketed a due date of February 14, 1996 for completion of the next step. RE33, ¶ 5.

Ms. Beckman created, administered, and sometimes even executed HGS's standardized docketing procedure for tracking actions respecting patent applications. Under the standardized procedure, the time allotted for completion of the process was at least ten weeks. RE33, ¶ 6. By contrast, the process was completed for the AIM-I application in about six weeks, reflecting the expedited procedure accorded AIM-I. RE33, ¶ 6. Ms. Beckman avers that each individual step taken by both Carella and HGS was completed within the standard allotted time, and in most cases much sooner. Indeed, Ms. Beckman avers that from January 31, 1996 until March 14, 1996, the AIM-I application was prepared with greater than usual diligence in the course of HGS's practice. RE33, ¶¶ 7-8.

A Declaration of Elliot M. Olstein further supports attorney diligence activities respecting AIM-I which inure to Dr. Ruben's benefit. RE43. Mr. Olstein, a member of the Carella firm since 1979, avers that he was the partner-in-charge of HGS matters, he had overseen the filing of more than one hundred patent applications on behalf of HGS, and he supervised the work of Mr. Herron and Mr. Ferraro, associates at Carella at that time. RE43, ¶ 1. Mr. Olstein, *inter alia*, avers to the dates and documents cited above. Mr. Olstein concludes by averring that, from the time Ms. Beckman contacted Carella on January 31, 1996 until the filing of the AIM-I application on March 14, 1996, Carella

handled the case on an expedited basis as requested by Ms. Beckman, i.e., the application was completed in significantly less time than was normally required. RE43.

x. Holidays, Vacations, and Weather-Related Closures

During the critical period, HGS observed the practice of being closed on Federal Holidays, and Ann Ferrie noted these closings in her laboratory notebooks. RE158, ¶ 214. HGS was also closed according to its usual practice for the entire week between Christmas and New Year's Day in December 1995. Moreover, the blizzard of January 1996 caused HGS (like the Federal Government) to close for four out of five days during the week of January 8-12, 1996. Ann Ferrie, who was primarily responsible for the hands-on benchwork of reducing AIM-I to practice, took only reasonable vacation time during the critical period, and spent one day packing and moving the laboratory, as averred to in her declaration (where she also lists the relevant dates and reasons for inactivity). RE158, ¶ 214.

b. Calendar of Diligence Activities

In summary, the activities described with particularity in this showing and the supporting exhibits demonstrate that Ruben was diligent during the entire critical period from just prior to June 29, 1995 through March 14, 1996. Specifically, the evidence shows that at least one activity, and often several, occurred daily in connection with the AIM-I invention during the entire critical period. A timeline (RE12), and a day-to-day calendar of activities (RE11) summarizing the critical period activities is provided herewith.

c. Contemporaneous Corroboration of Ruben's Invention

Ann Ferrie has explained the communications from Dr. Ruben to her in February 1994 and thereafter which corroborate Dr. Ruben's conception of antibodies that (1) specifically bind the AIM-I protein having apoptosis-inducing activity and (2) could be used in the treatment of autoimmune disease. RE158, ¶ 9. Ferrie's experiments and her laboratory notebook records thereof corroborate Dr. Ruben's diligence until either (a) an actual reduction to practice by August 31, 1995 or (b) a constructive reduction to practice on March 14, 1996. RE158. RE87-95. Application of the "rule of reason" to all of the facts proved by Ruben in this showing establishes by more than a preponderance of the evidence that conception and diligence were each contemporaneously corroborated. Corroboration of Ruben's conception and diligence is also provided by the activities and documentary records of the organized research effort ongoing between HGS and SB, viz., the Joint Program.

IV. RUBEN HAS SHOWN *PRIMA FACIE* ENTITLEMENT TO PRIORITY OF INVENTION PRIOR TO THE EARLIEST POSSIBLE EFFECTIVE DATE OF WILEY'S '228 PATENT

Ruben has demonstrated that he conceived prior to June 29, 1995 and was reasonably diligent from a time just prior to June 29, 1995 until either (a) an actual reduction to practice by August 31, 1995 or (b) a constructive reduction to practice on March 14, 1996, the filing date of the '405 priority application. Accordingly, Ruben is *prima facie* entitled to judgment, relative to patentee, on the basis of priority of invention.

V. RUBEN'S SHOWING OF COMPLIANCE WITH 35 U.S.C. § 135(b)

Ruben's pending claims, 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27, were originally filed on September 16, 2003 in the captioned '431 application. Thus all of claims 1-2, 6, 8-10, 13-14, 17-18, 20-24, and 26-27 were pending prior to the February 18, 2004 anniversary date of the '228 patent issuance. Accordingly, Ruben is in full compliance with the provisions under 35 U.S.C. § 135(b).

VI. CONCLUSION

In view of the above showing that Ruben is *prima facie* entitled to judgment based on priority of invention under 35 U.S.C. § 102(g) relative to the earliest possible effective filing date of Wiley Patent No. 6,521,228 (i.e. June 29, 1995), Ruben respectfully requests that an interference be declared on the subject matter of RUBEN PROPOSED COUNT A involving the captioned application and U.S. Patent No. 6,521,228.

Respectfully submitted,

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